London 10 December 2015

Low level transaminitis in an HIV mono-infected patient

Emmanuel A. Tsochatzis

Senior Clinical Lecturer and Consultant Hepatologist

UCL Institute of Liver and Digestive Health
Royal Free Hospital

Talk outline

Causes of transaminitis

NAFLD

Epidemiology

Prognosis

Who needs referral to the hepatologist

Treatment

Liver disease in HIV mono-infection

- Drug toxicity
- Alcohol
- Nodular regenerative hyperplasia/NCPH
- NAFLD

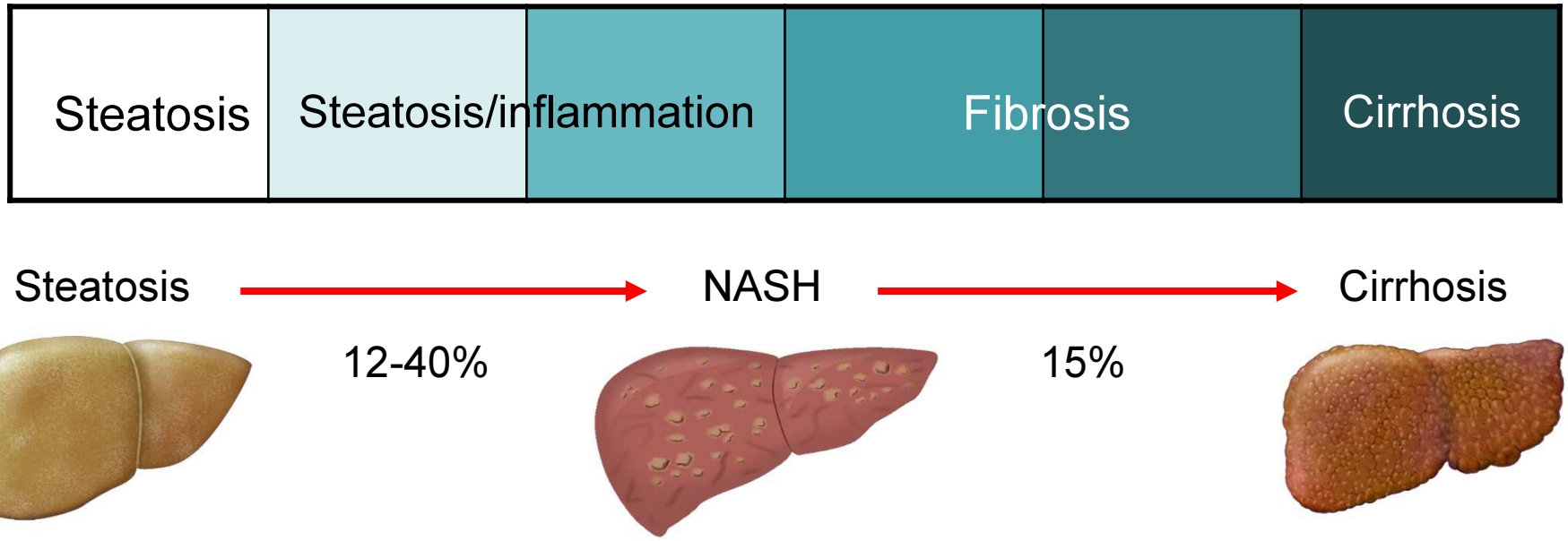
Drug toxicity

- Metabolic host-mediated (intrinsic and idiosyncratic)
- Hypersensitivity (early occurrence)
- Mitochondrial toxicity (prolonged exposure)
- Didanosine/stavudine more consistently associated with advanced fibrosis

Soriano 2008; Blanco 2011; Mendeni 2011

What is NAFLD ?

- Non-Alcoholic Fatty Liver Disease
- Wide disease range from simple steatosis to cirrhosis

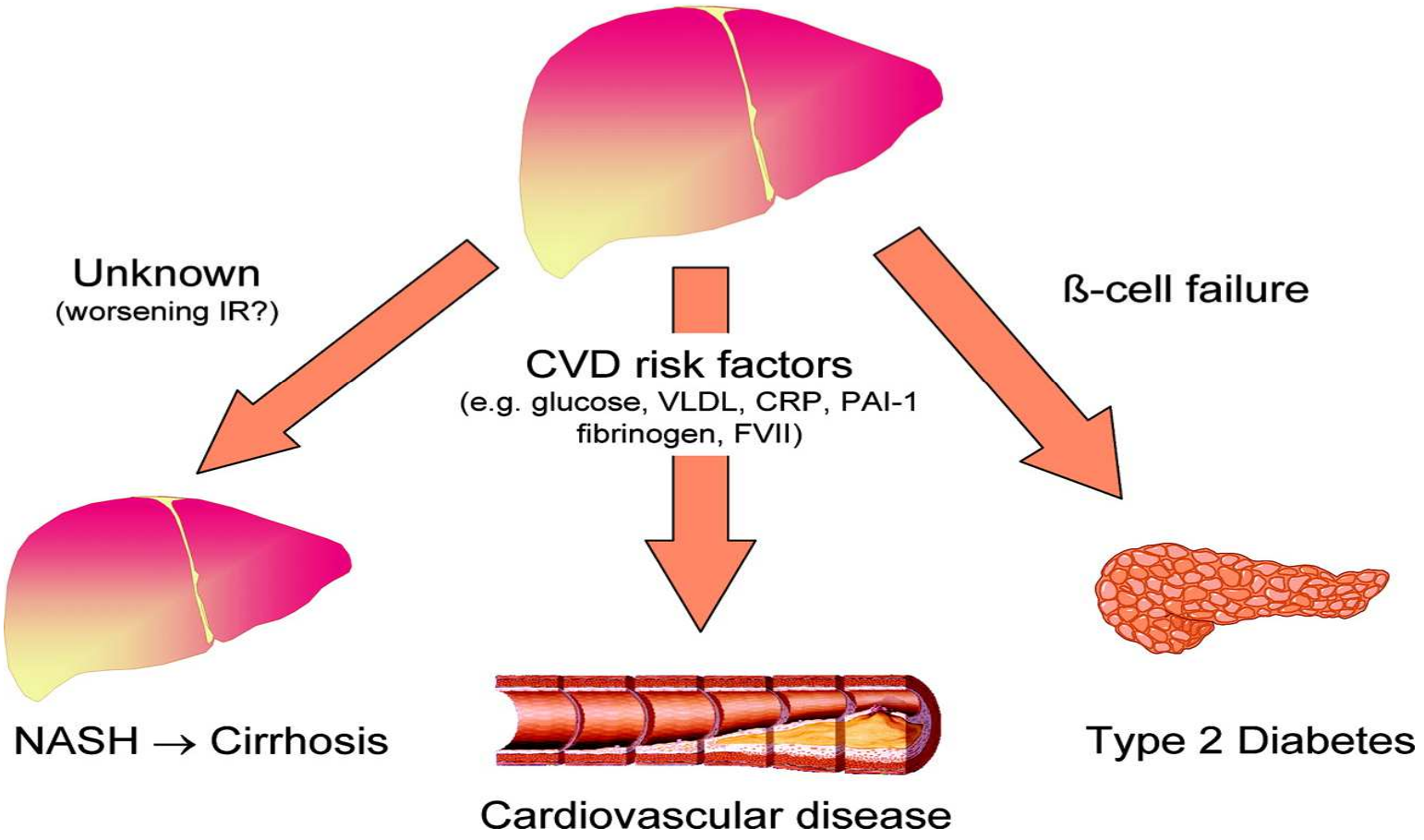


Definition

- Only recently recognized (Ludwig, 1980)
- Liver steatosis in people who do not use alcohol

  (<20 g/d M, <10 g/d F)
- Underlying diagnosis of >60% “cryptogenic” cirrhosis
- Hepatic manifestation of the metabolic syndrome

NAFLD: Potential consequences



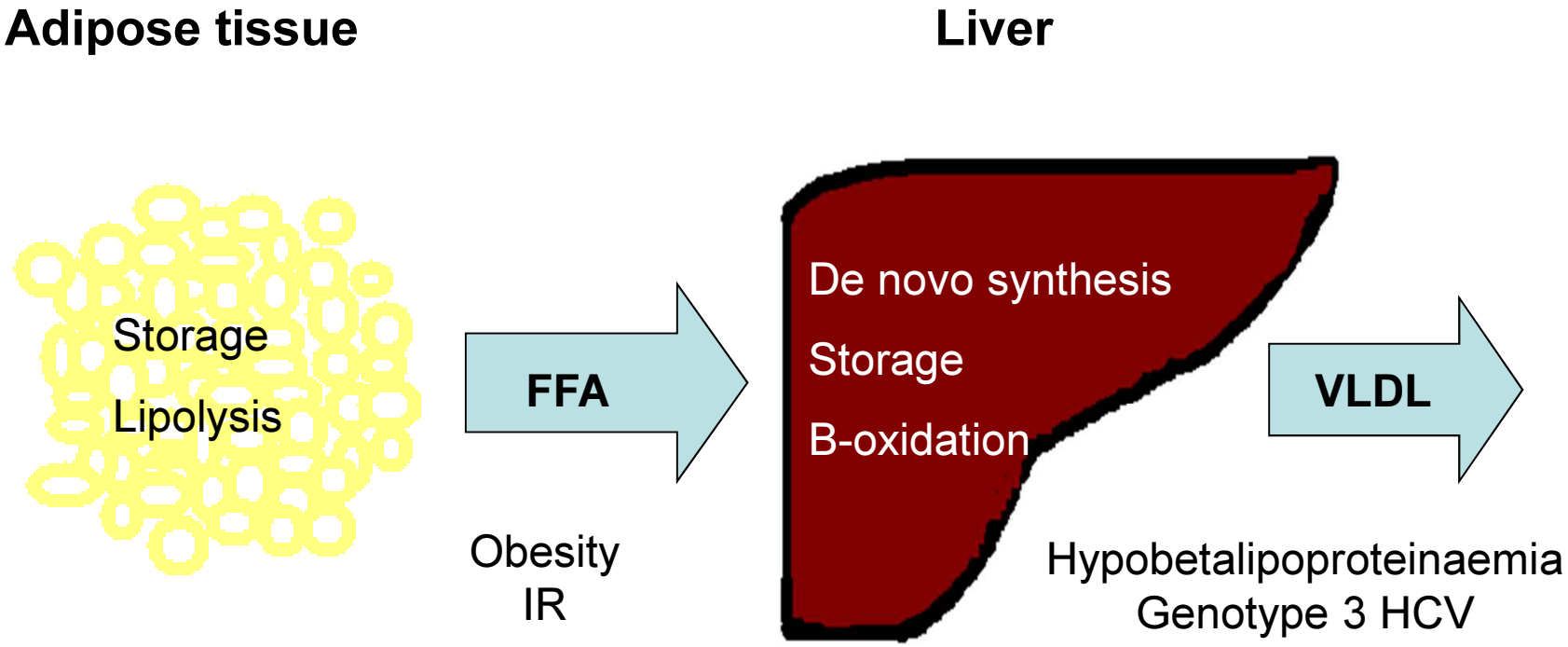
Kotronen, Arterioscler Thromb Vasc Biol 2008

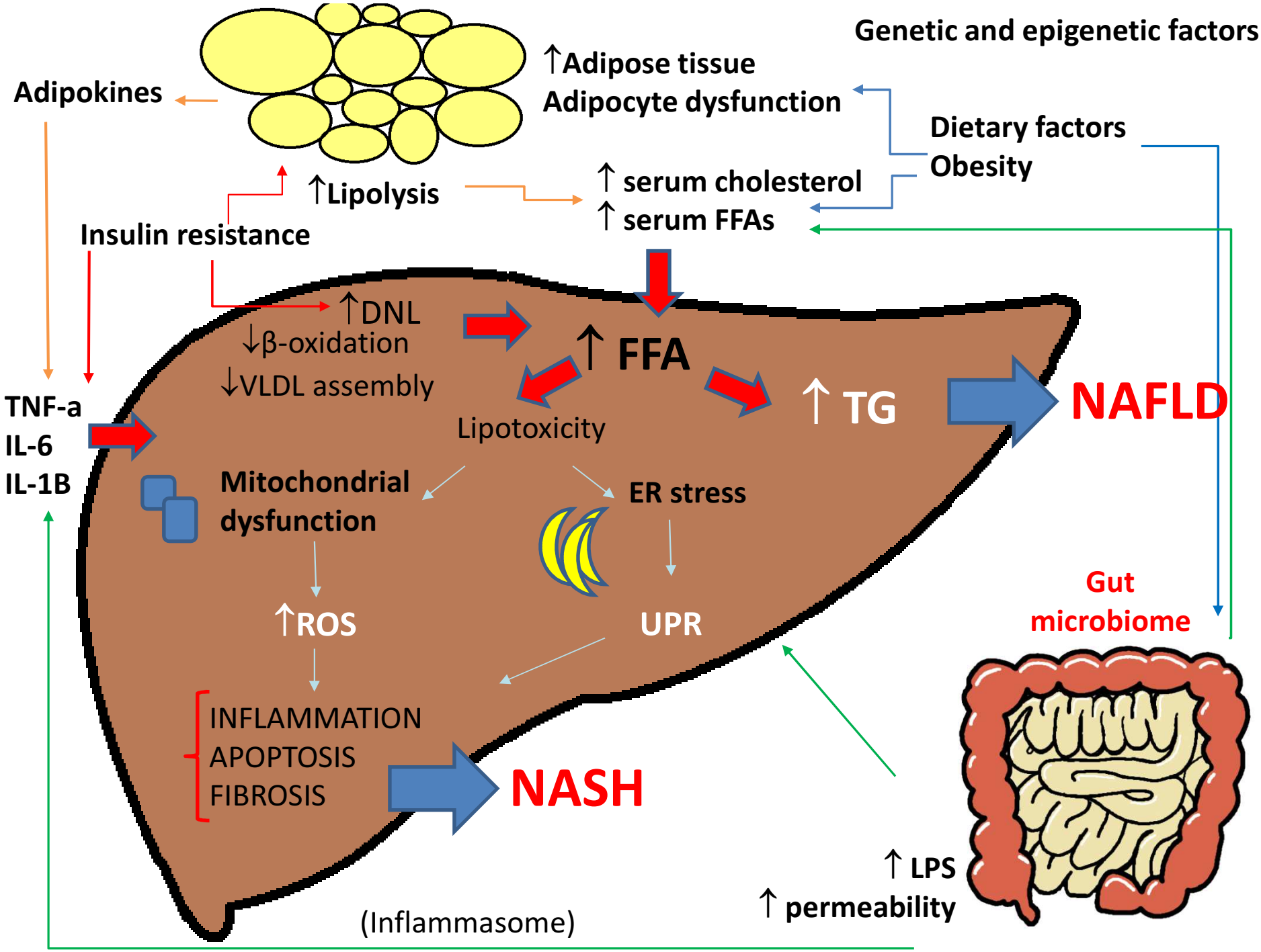
Pathophysiology

Pathophysiology

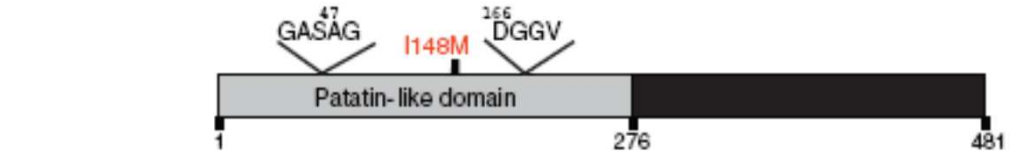
- Multifactorial
- Genetic factors
- Nutritional factors
- Lifestyle

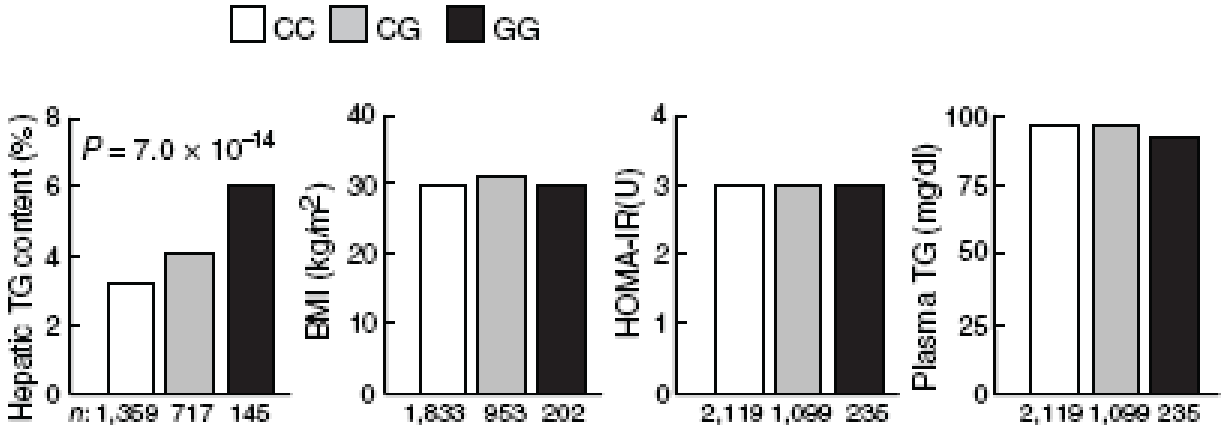
Imbalance in lipid influx/synthesis and oxidation/excretion




Genetic and epigenetic factors
↑Adipose tissue
Adipocyte dysfunction
Adipokines
Dietary factors
Obesity
↑Lipolysis
↑ serum cholesterol
↑ serum FFAs
Insulin resistance
↑DNL
↓β-oxidation
↓VLDL assembly
↑ FFA
↑ TG
NAFLD
TNF-a
IL-6
IL-1B
Lipotoxicity
Mitochondrial dysfunction
ER stress
↑ROS
UPR
Gut microbiome
INFLAMMATION
APOPTOSIS
FIBROSIS
NASH
↑ LPS
↑ permeability
(Inflammasome)

Genetic factors- adiponutrin (PNPLA3)



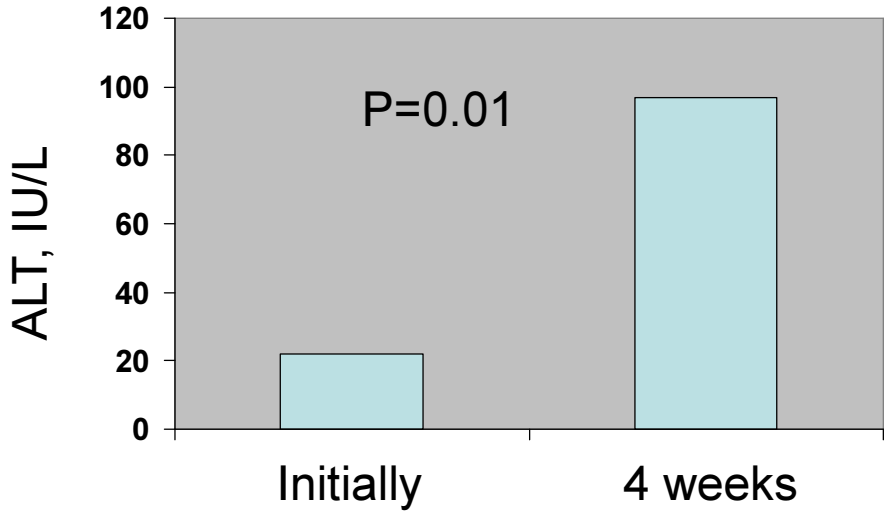


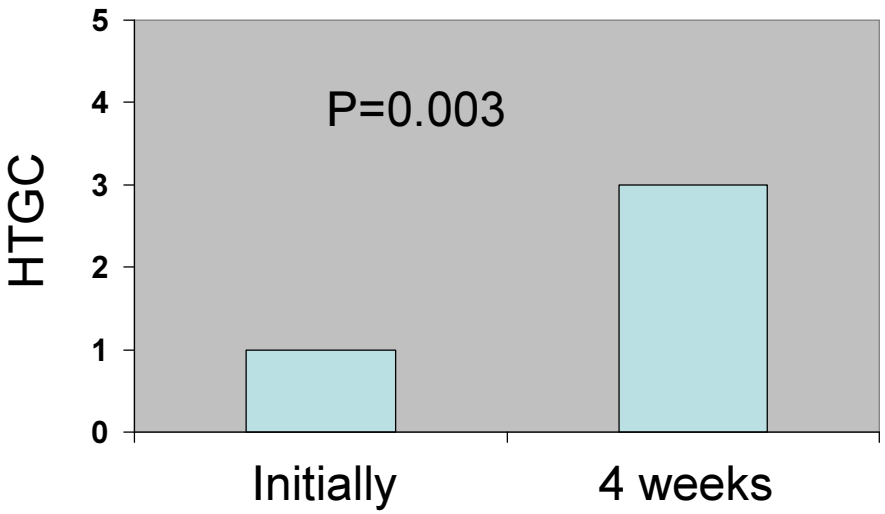
2111 patients
9229 SNPs

Romeo, Nature Genetics 2008

Nutrition and NAFLD

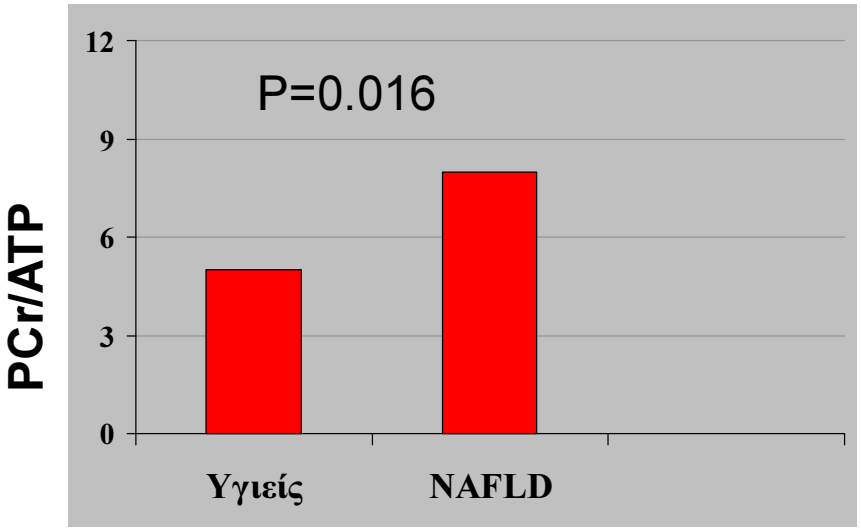
- 18 healthy volunteers
- 4 week course of double calories, fast food meals, no exercise

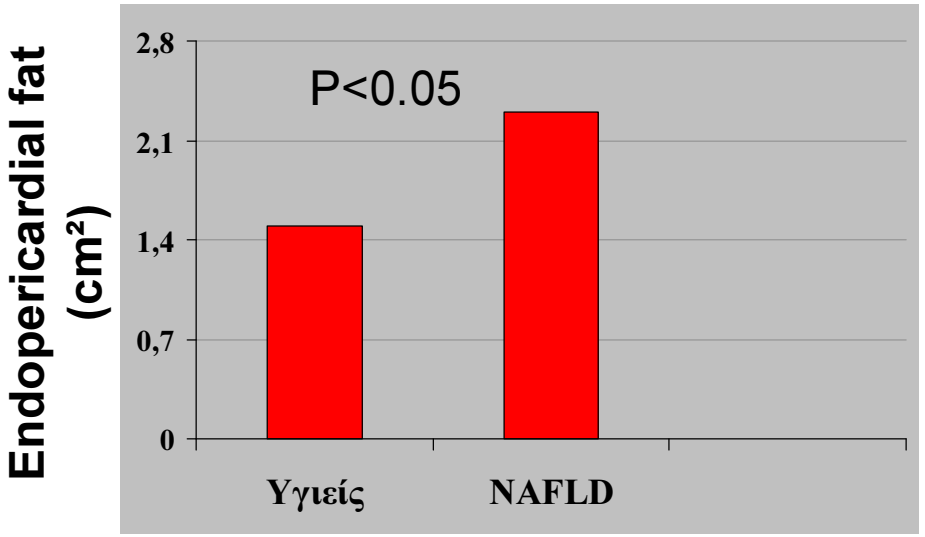


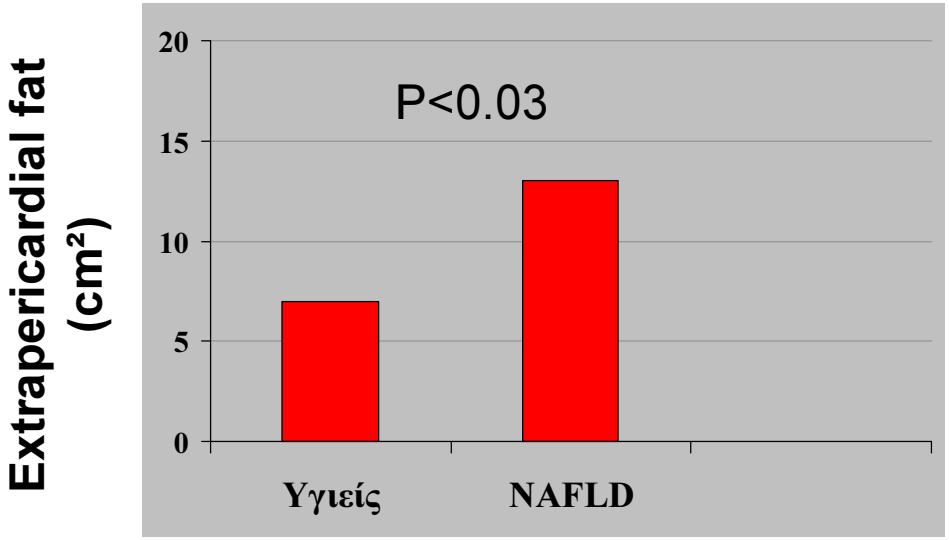


Kechagias, Gut 2008

NAFLD and cardiac metabolism



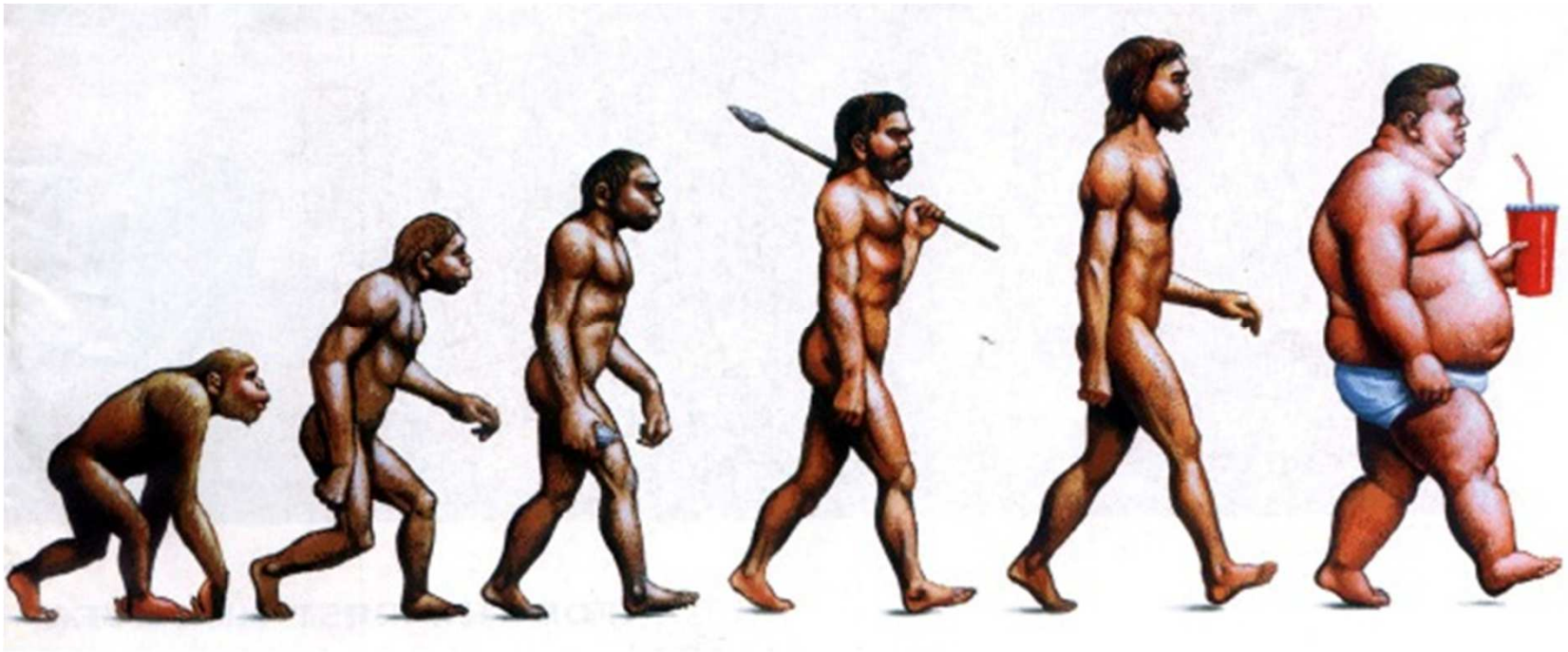




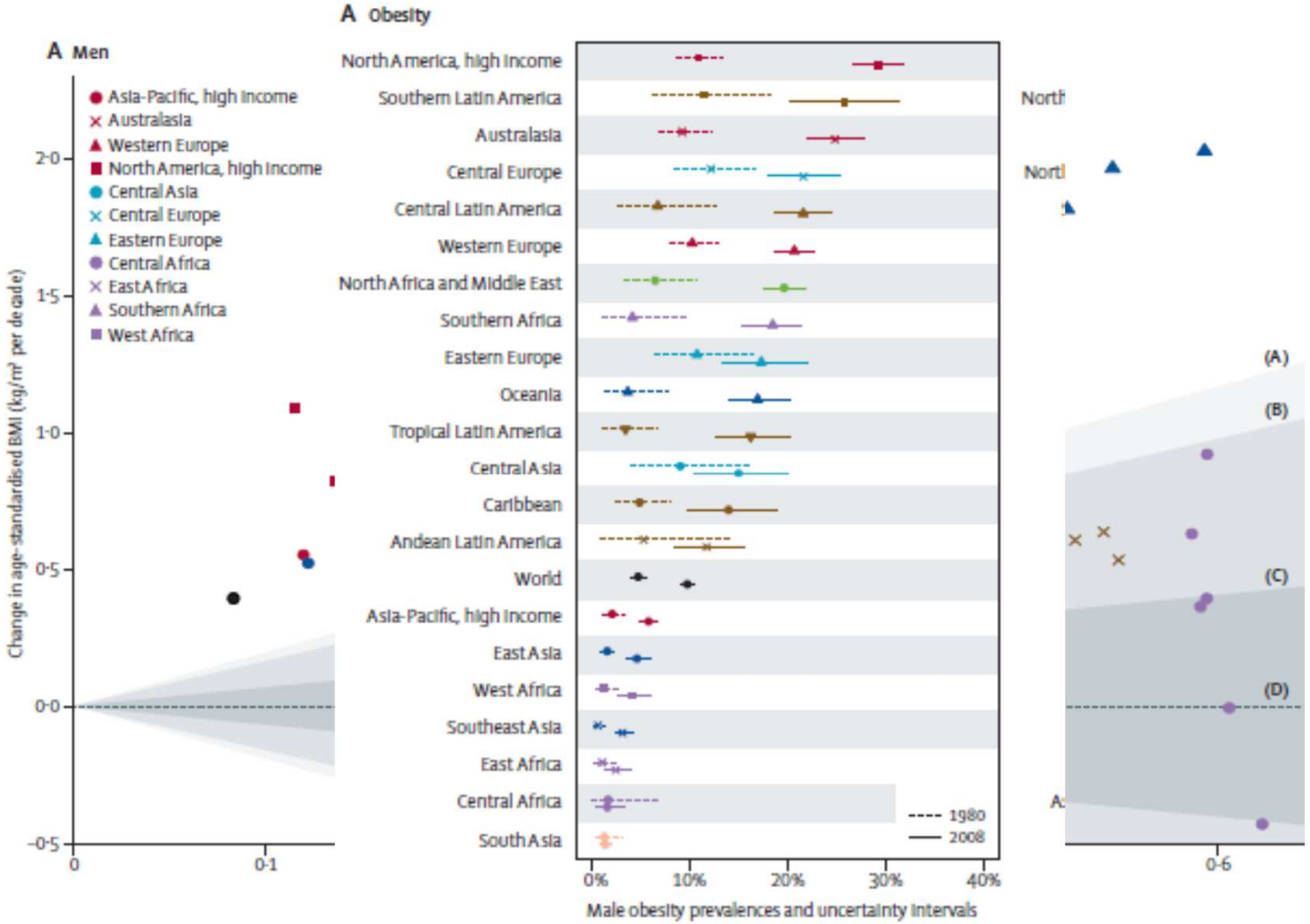
21 NAFLD vs 21 controls
Mean age 35 years

Perseghin, Hepatology 2008

Epidemiology



Growing prevalence of obesity



Finucane Lancet 2011

Increasing prevalence of MS in HIV

Table 3. Proportion of individuals meeting each definition of the metabolic syndrome in each of the six calendar periods, according to the analytical approach used.

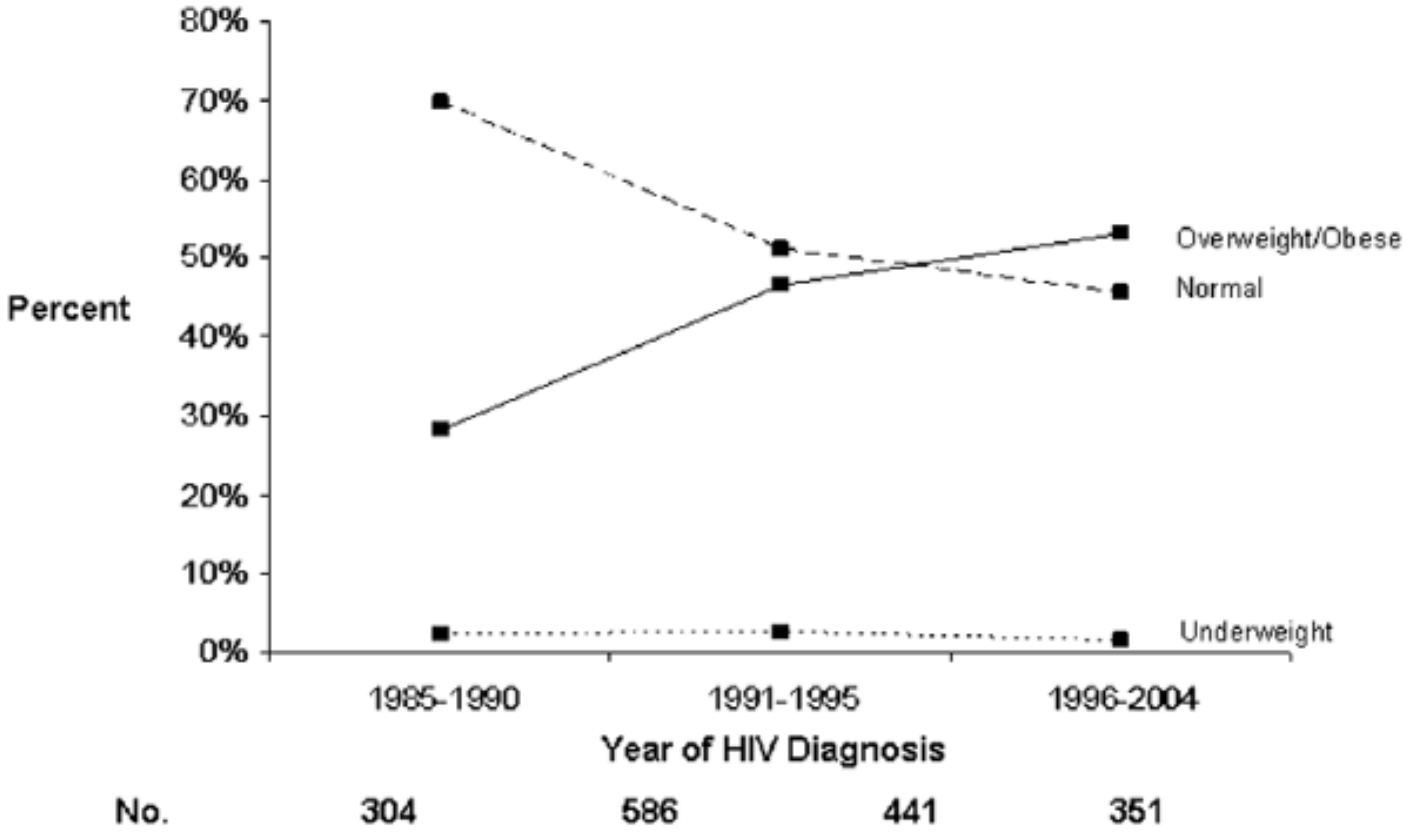
		Calendar period					
	Study entry	2000/2001	2002	2003	2004	2005	2006/2007
Definition 1: Main analyses							
Number of patients included in analysis	33347	24349	26615	28449	28661	26265	23853
% meeting the definition	7.3	19.4	23.8	26.9	31.8	35.9	41.6
Definition 2: Inclusion of LLT and antihypertensive medications							
Number of patients included in analysis	33347	24349	26615	28449	28661	26265	23853
% meeting the definition	8.7	21.2	25.7	29.0	34.1	38.2	44.1
Definition 3: Information required on ≥3 of 5 components							
Number of patients included in analysis	27853	22504	24662	26399	27158	25036	22942
% meeting the definition	8.8	20.9	25.7	29.0	33.6	37.6	43.2
Definition 4: Components reversible, missing = absent							
Number of patients included in analysis	33347	24349	26615	28449	28661	26265	23853
% meeting the definition	5.5	9.6	10.8	11.2	12.7	13.7	15.3
Definition 5: Components reversible, laboratory measurements in the previous 12 months							
Number of patients included in analysis	27310	20282	23552	25598	26651	24758	22721
% meeting the definition	6.2	9.2	10.1	10.2	11.2	11.8	11.7
Definition 6: Two consecutive laboratory values above (below) threshold							
Number of patients included in analysis	33347	24349	26615	28449	28661	26265	23853
% meeting the definition	4.0	9.8	12.0	13.8	16.4	18.6	21.1

LLT, lipid-lowering therapy.

33,347 patients – MS from 8.7% to 44.1% in 7 years

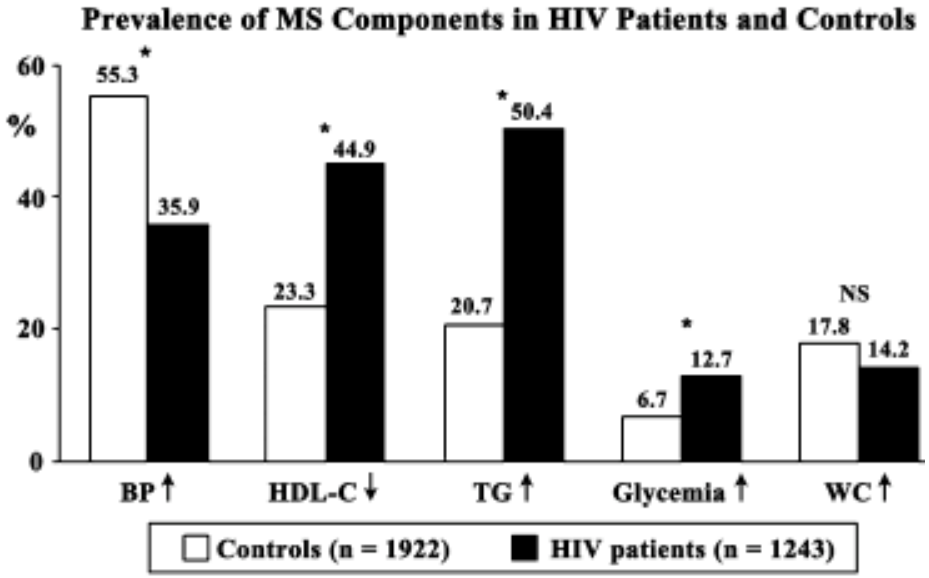
Worm AIDS 2010

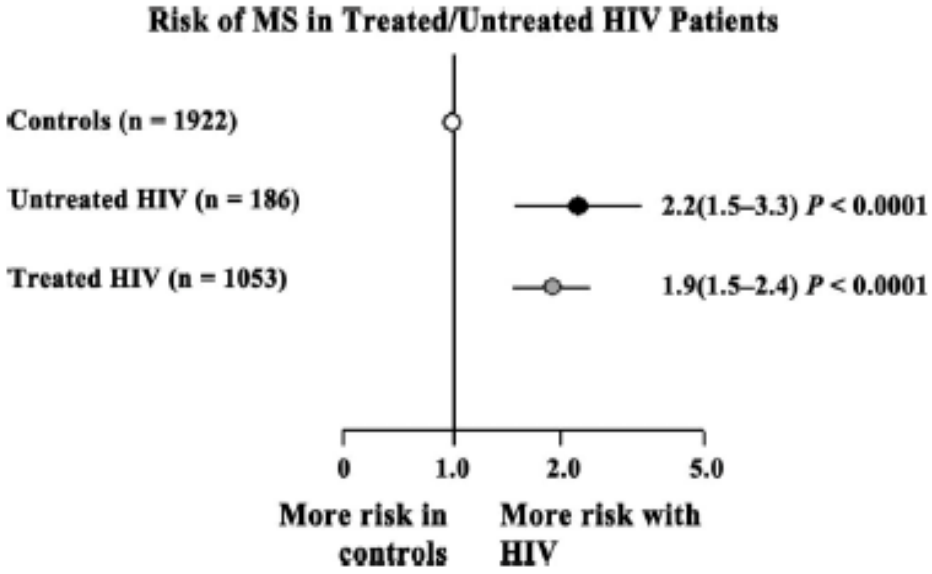
Obesity in HIV patients



Crum-Cianflone 2010

MS more prevalent in HIV than controls



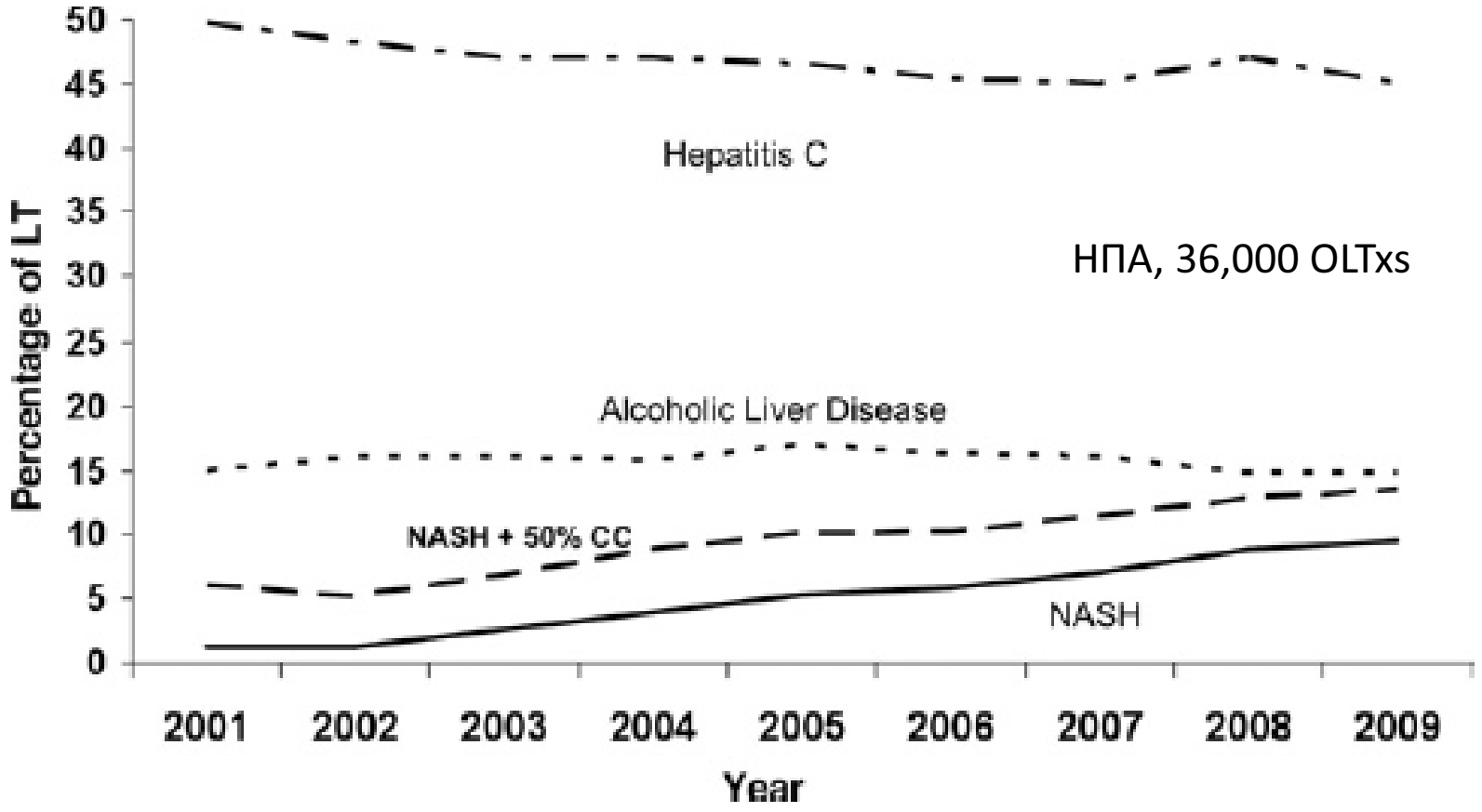


Bonfanti 2007

Non alcoholic fatty liver disease (NAFLD)

- Prevalence 20-25% of the general population
- Estimated 40-60% in patients with HIV
- 2-7% has steatohepatitis (NASH)
- Hepatic manifestation of metabolic syndrome
- >50% of secondary care referrals due to NAFLD

NASH and liver transplantation



НПА, 36,000 OLTxs

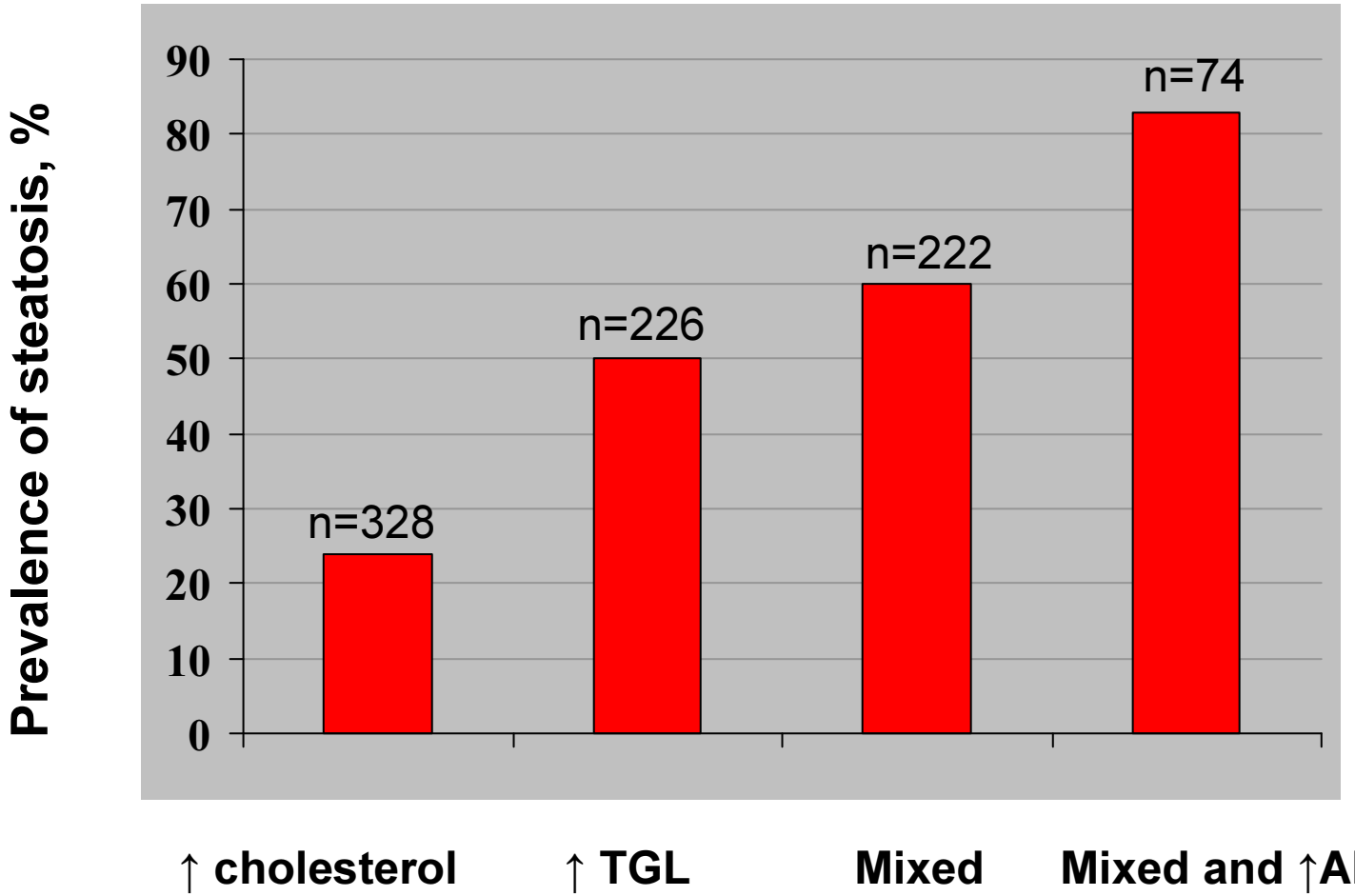
2020-25: NASH main indication for OLTx

Charlton Gastro 2011

Factors associated with progression

- Age (mitochondrial dysfunction)
- All metabolic syndrome components
  - Obesity/increased WC
  - T2DM
  - Hypertension
  - Dyslipidaemia
- Smoking

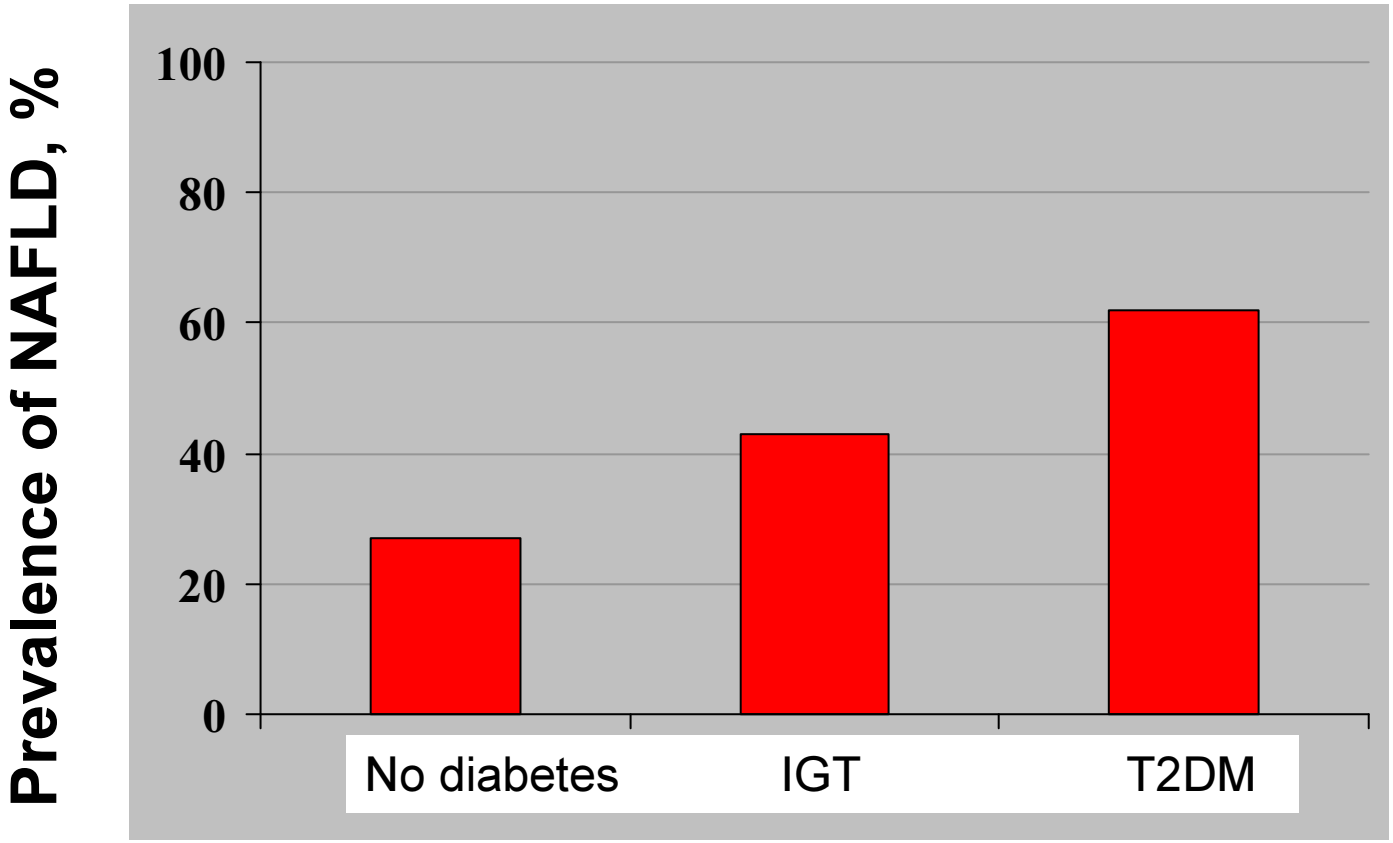
Hyperlipidaemia and NAFLD



Dallas Heart study, 2124 patients

Browning, Hepatology 2006

T2DM and NAFLD



1950 patients
566 NAFLD (U/S)

Jimba, Diabet Med 2005

NASH in HIV patients

NASH in HIV patients

1. HAART treatment

NRTIs, thymidine analogues (IR), didanosine (mitochondrial toxicity)

2. Lipodystrophy

3. HIV virus

Mitochondrial damage, lipid levels

NASH in HIV patients

- 128 consecutive HIV mono-infected patients
- Mean BMI 24.5 kg/m^2
- 55% NAFLD on US
- 18% Fibroscan >7.4 Kpa
- Age and MS independent predictors of >7.4 KPa

Lombardi, manuscript in preparation

NASH in HIV patients

APRI>1.5 in 8.3% of 432 patients

T2DM and detectable HIV viraemia independent predictors

Cohort also included patients who used alcohol

DallaPiazza BMC Infect Dis 2008

Abnormal LFTs in HIV mono-infection

- 156/2398 (6.5%) patients persistently increased LFTs
- 97% on treatment
- US in 42%, of which 71% had steatosis
- FIB4>1.45 in 33%, >3.25 in 4%
- Liver biopsy in 20 patients
- 13/20 had NASH, one had cirrhosis

Lombardi, manuscript in preparation

Laboratory findings

Laboratory findings

- Increased ALT (<4xULN), ALT>AST (dd from ALD)
- Increased GGT less often
- Increased ferritin
- Low titres of ANA or ASMA (10-15%)

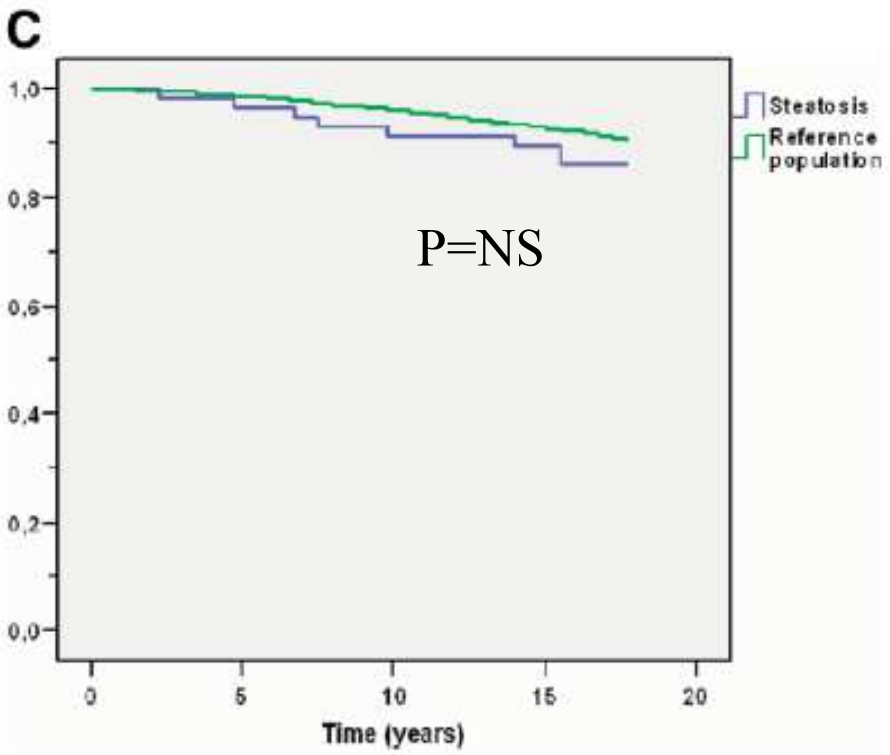
NAFLD – systemic disease

- Manifestation of lipotoxicity
- Low degree of systemic inflammation (60% ↑ferritin)
- Endothelial dysfunction
- ↑carotid intima media thickness
- Coagulation abnormalities (↑TF, factor VII)
- Cardiac metabolism abnormalities

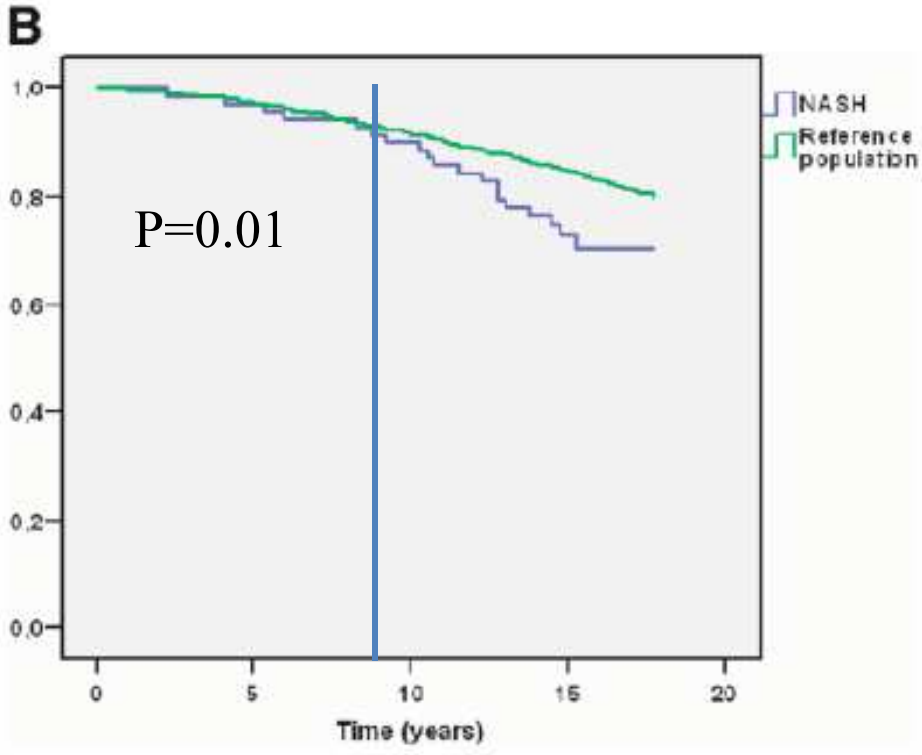
Villanova, Hepatology 2005
Sanyal, AASLD 2007

Prognosis – hepatology referrals

Natural history of NAFLD



Simple steatosis

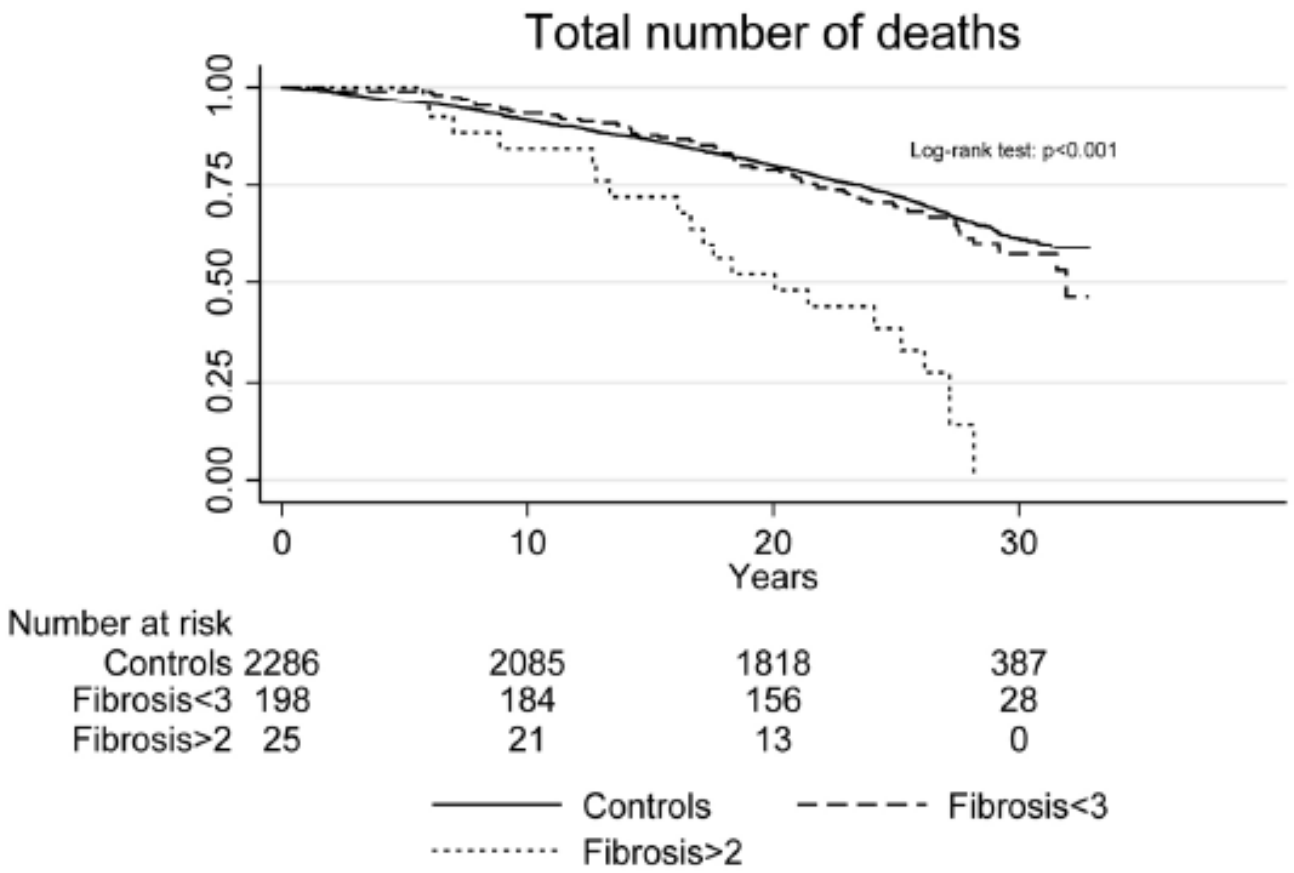


NASH

129 patients
Mean follow-up 13.7 years

Ekstedt, Hepatology 2006

Natural history of NASH



Ekstedt Hepatology 2015

NASH and mortality

- CVS main cause of death
- Liver disease only 3d cause of mortality

Ekstedt, Hepatology 2006
Soderberg, Hepatology 2010

NAFLD – referral pathways

- High prevalence, low severity
- No liver-specific treatment
- How to select patients for referral?
- Non-invasive fibrosis assessment

Simple non-invasive clinical scores for F>2

- **FIB4**

  Age, ALT, AST, PLT

- **NAFLD fibrosis score**

  Age, BMI, hyperglycemia, AST/ALT, PLT, albumin

Angulo Hepatology 2007 Shah Clin Gastroenterol Hepatol 2009

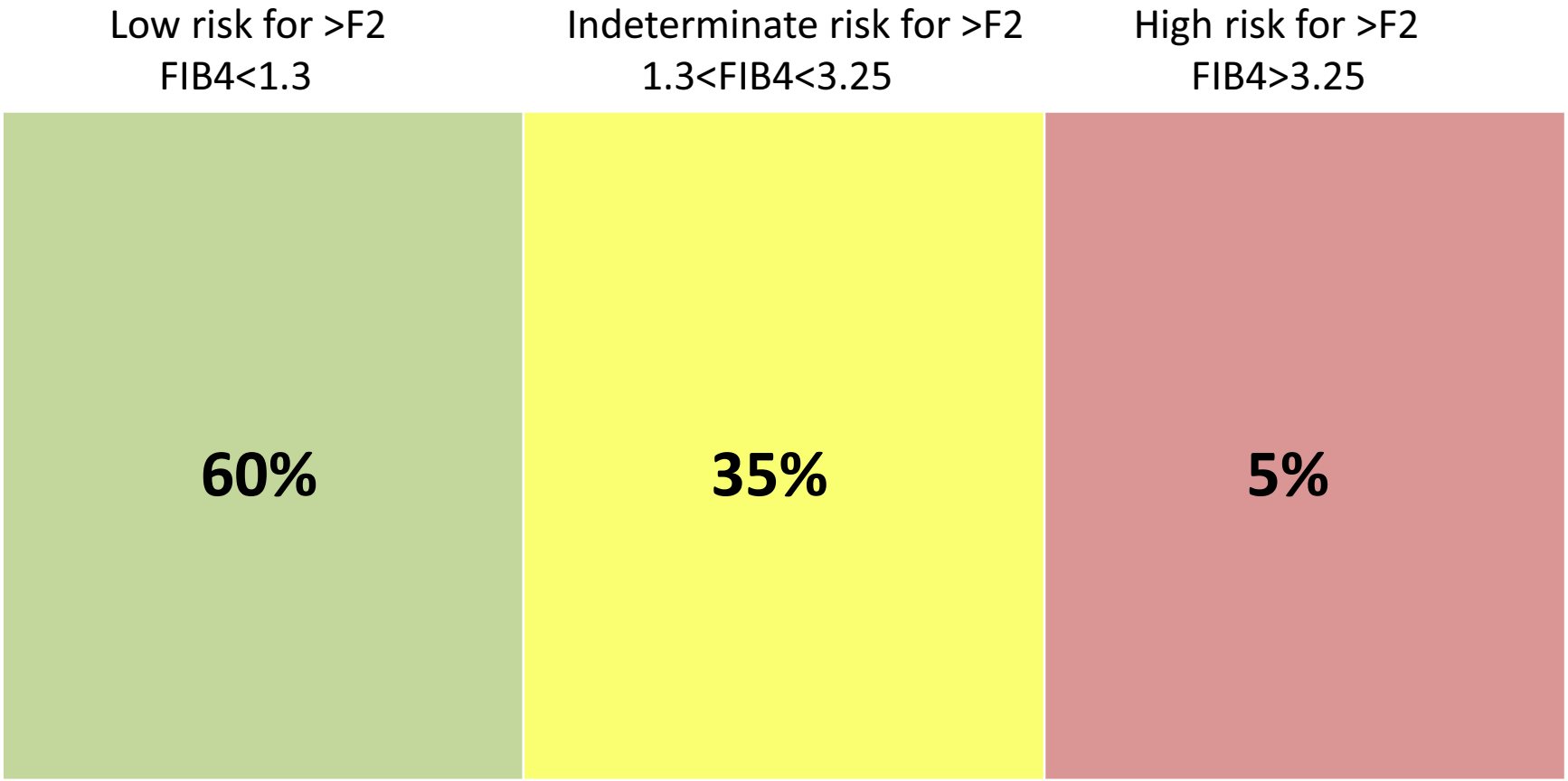
Calculation of simple NITs

FIB-4: http://gihep.com/?page_id=9

NAFLD fibrosis score: http://nafldscore.com

Liver calculator Free application for smartphones

Risk classification according to simple NITs

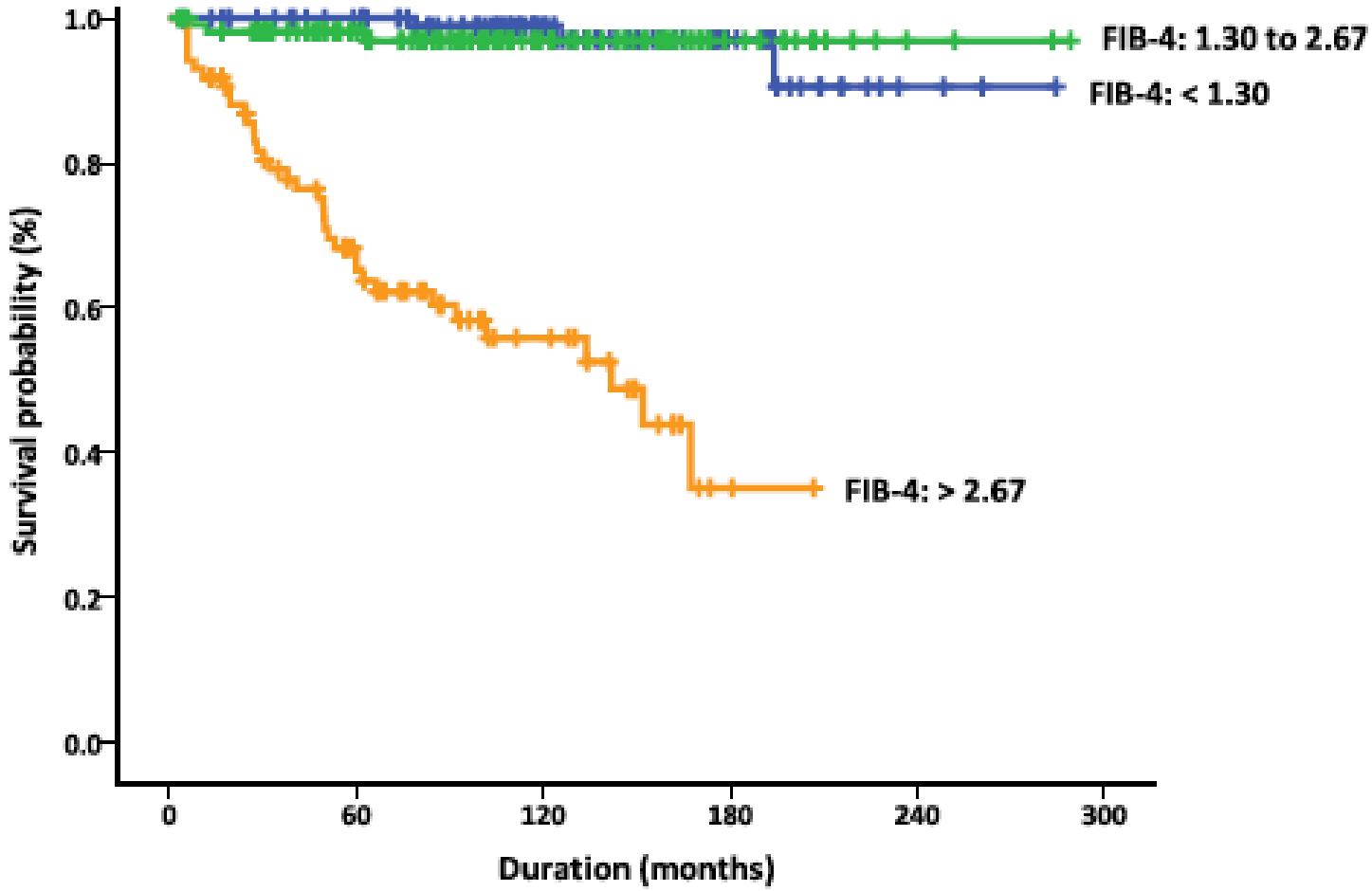


NITs and prognosis

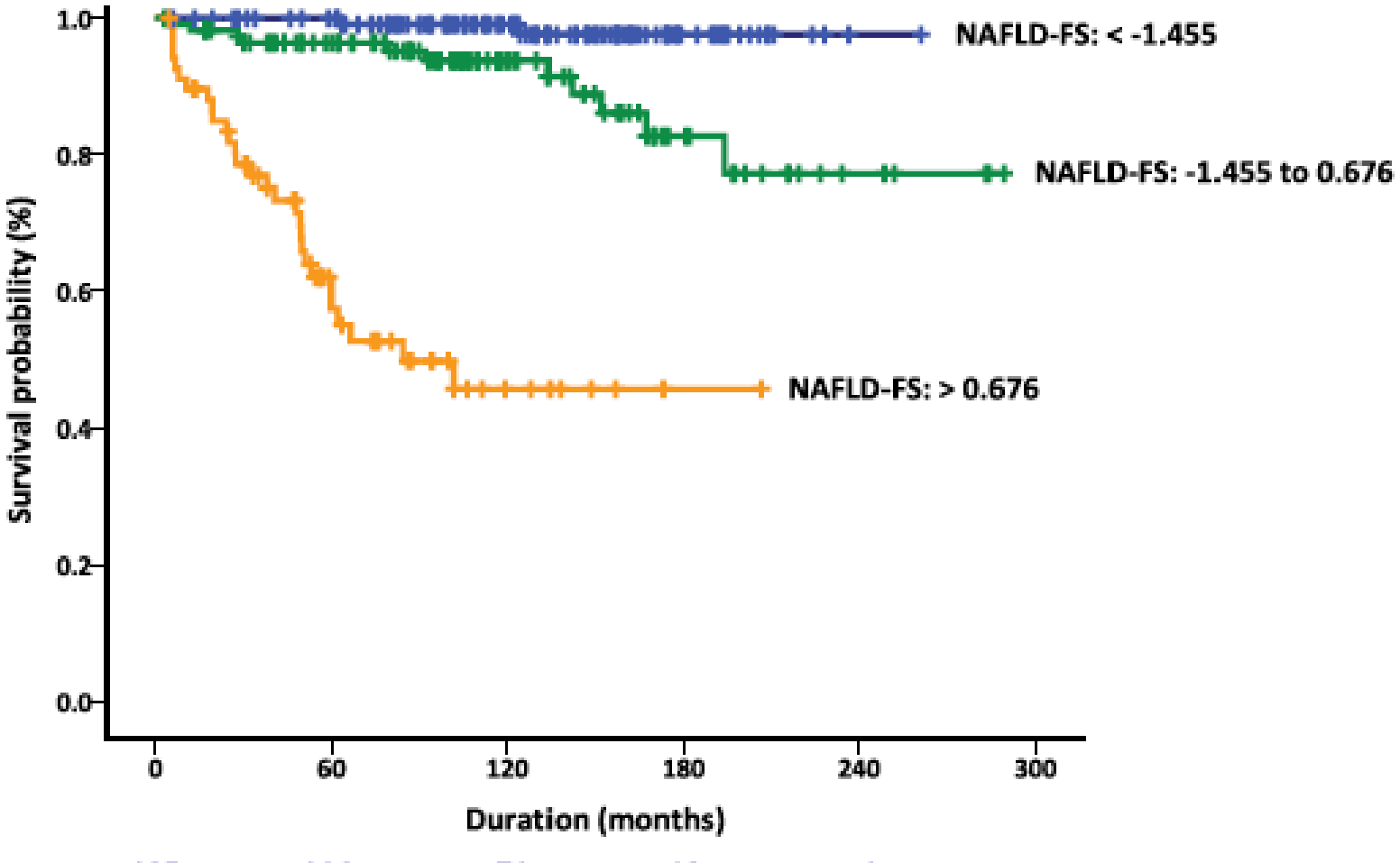
- NITs initially developed as surrogate markers of fibrosis with a view to replace LB

- Increasingly used to assess prognosis

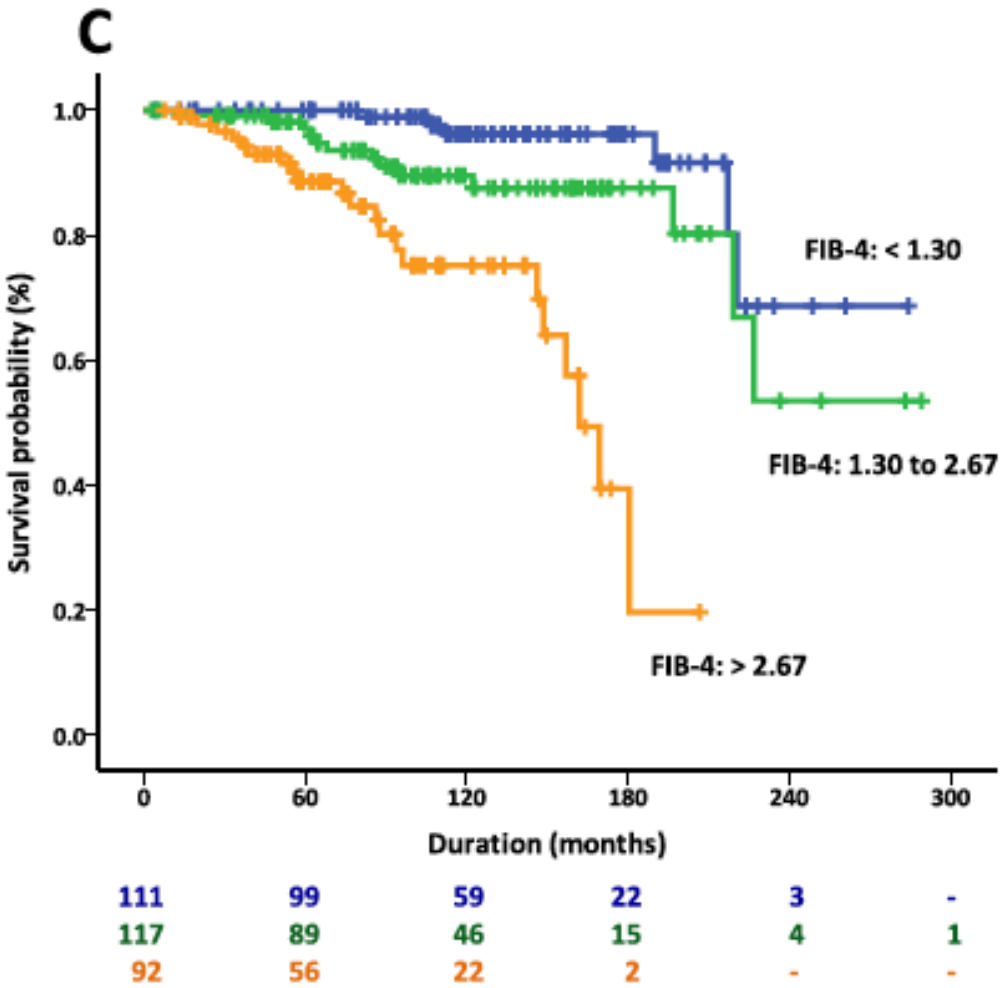
Cumulative liver related events

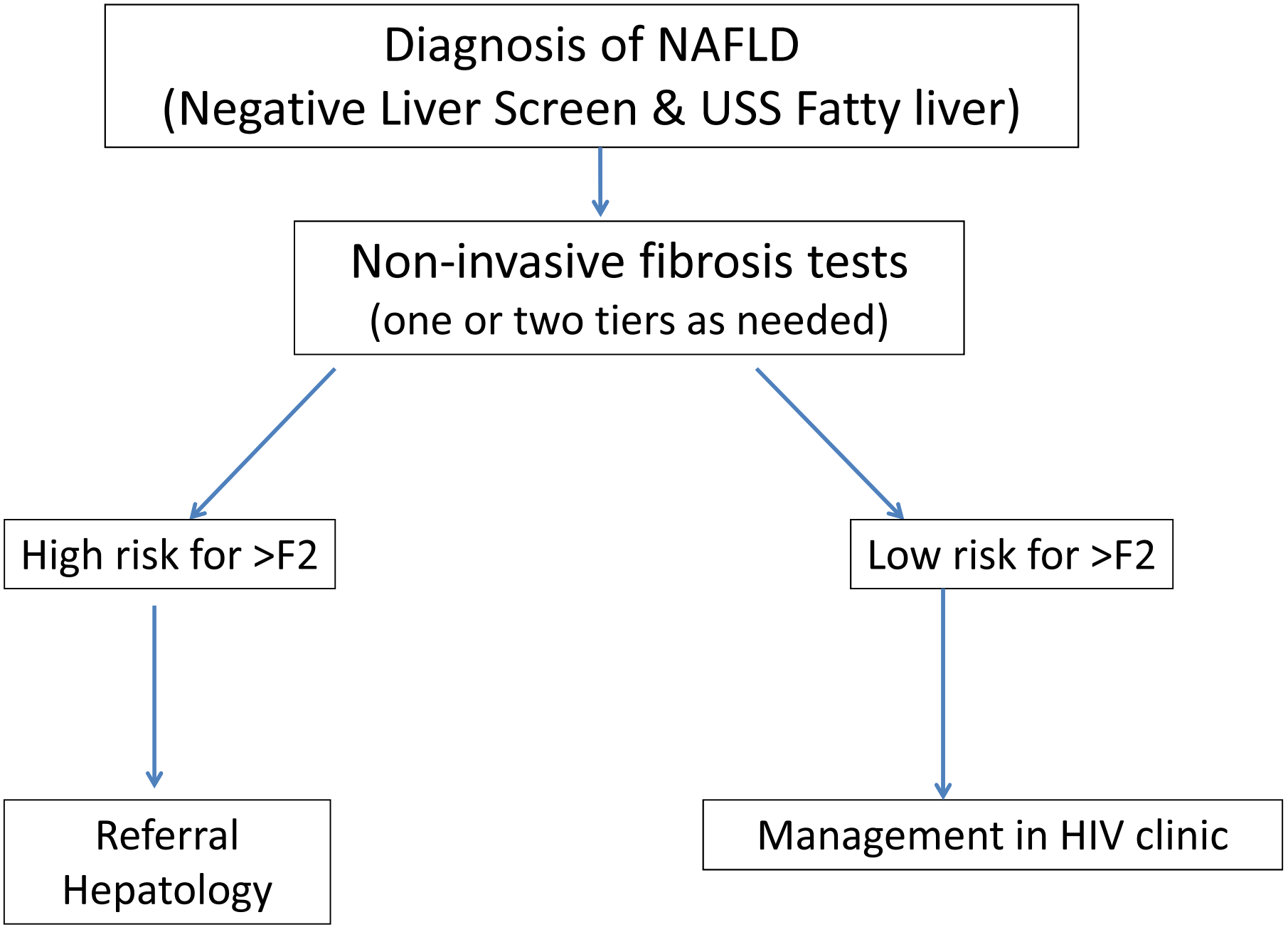


Cumulative liver related events



Cumulative death



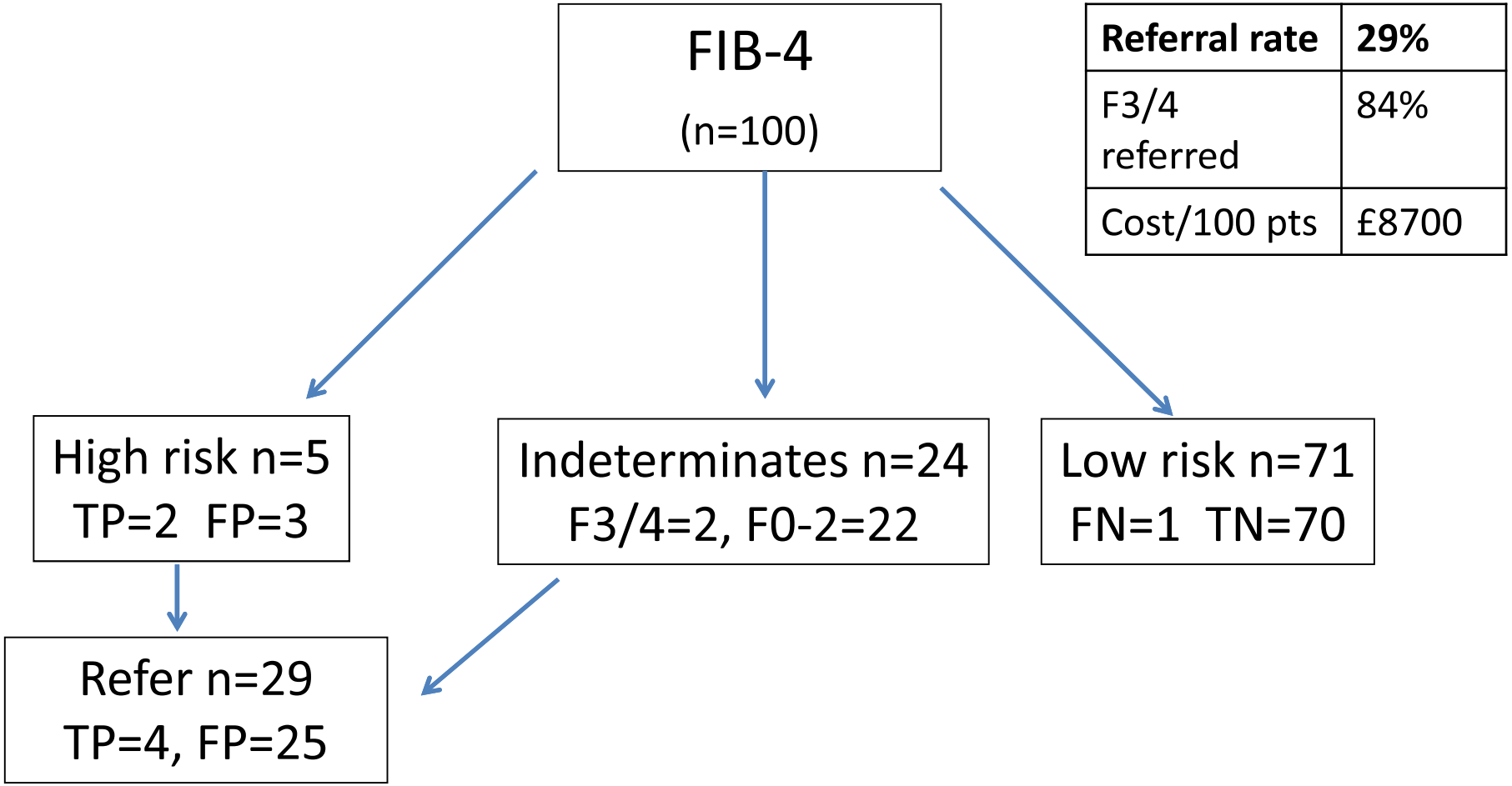

Diagnosis of NAFLD
(Negative Liver Screen & USS Fatty liver)
Non-invasive fibrosis tests
(one or two tiers as needed)
High risk for >F2
Low risk for >F2
Referral
Hepatology
Management in HIV clinic

Summary se and sp of NIT for NAFLD

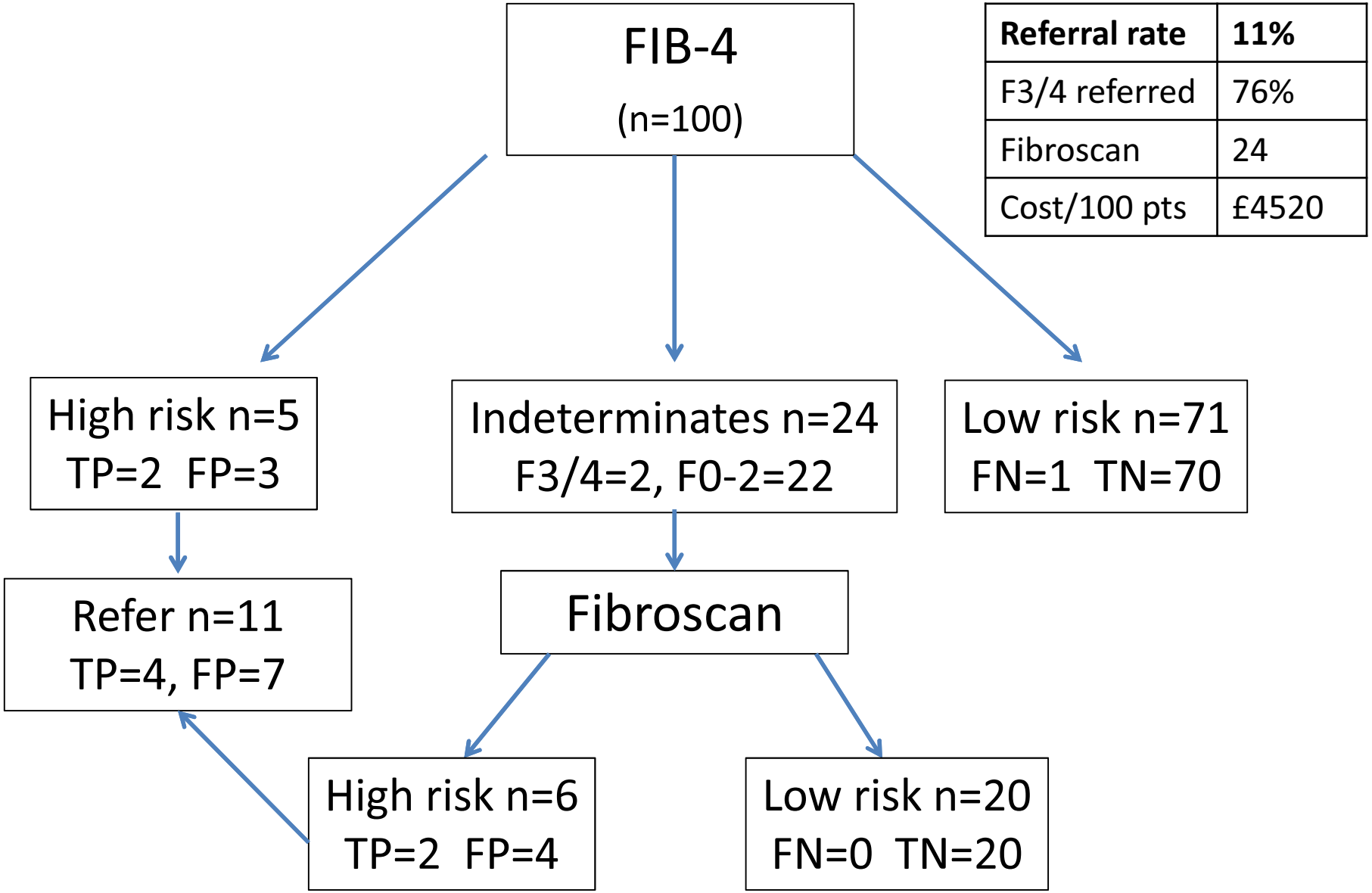
Test	Cut-off	Sensitivity	Specificity	NPV TN/(TN+FN)	Indeter-minates	High
NFS (n=10)	-1.455, 0.676	80%	66%	98.4%	31	5
FIB4 (n=4)	1.30, 3.25	84%	74%	98.5%	24	5
BARD (n=7)	>2	84%	61%	98.6%	_	41
ELF (n=1)	10.3	80%	90%	98.8%	_	14
Fibrotest (n=3)	8.7-9.8	88%	73%	99.1%	24	6
Fibroscan (n=8)	0.3, 0.7	82%	84%	98.9%	-	19

Estimated prevalence of advanced fibrosis (F3 and above) is 5%.

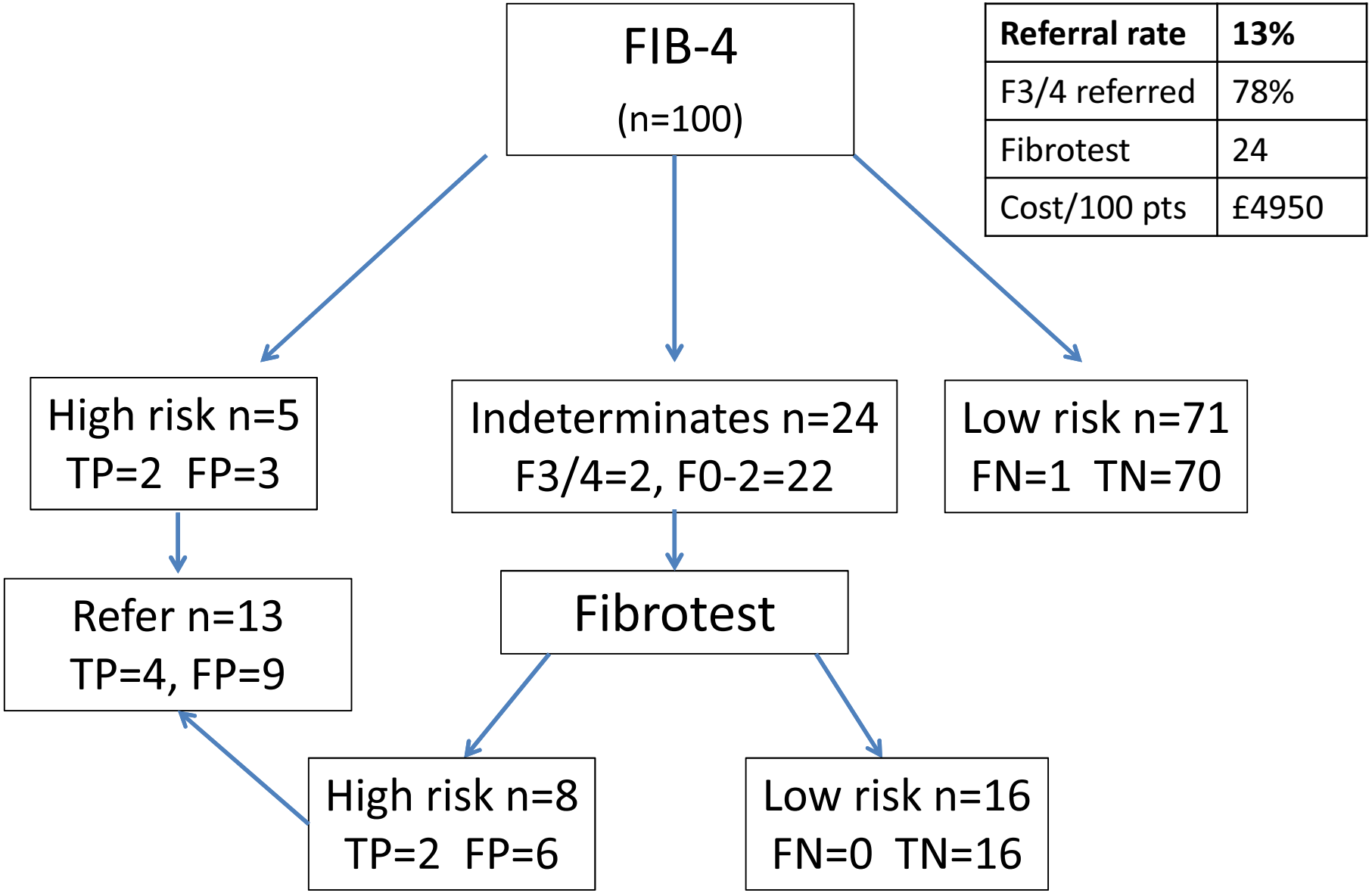
Columns 6 and 7 are based on testing 100 patients and indicate the number of



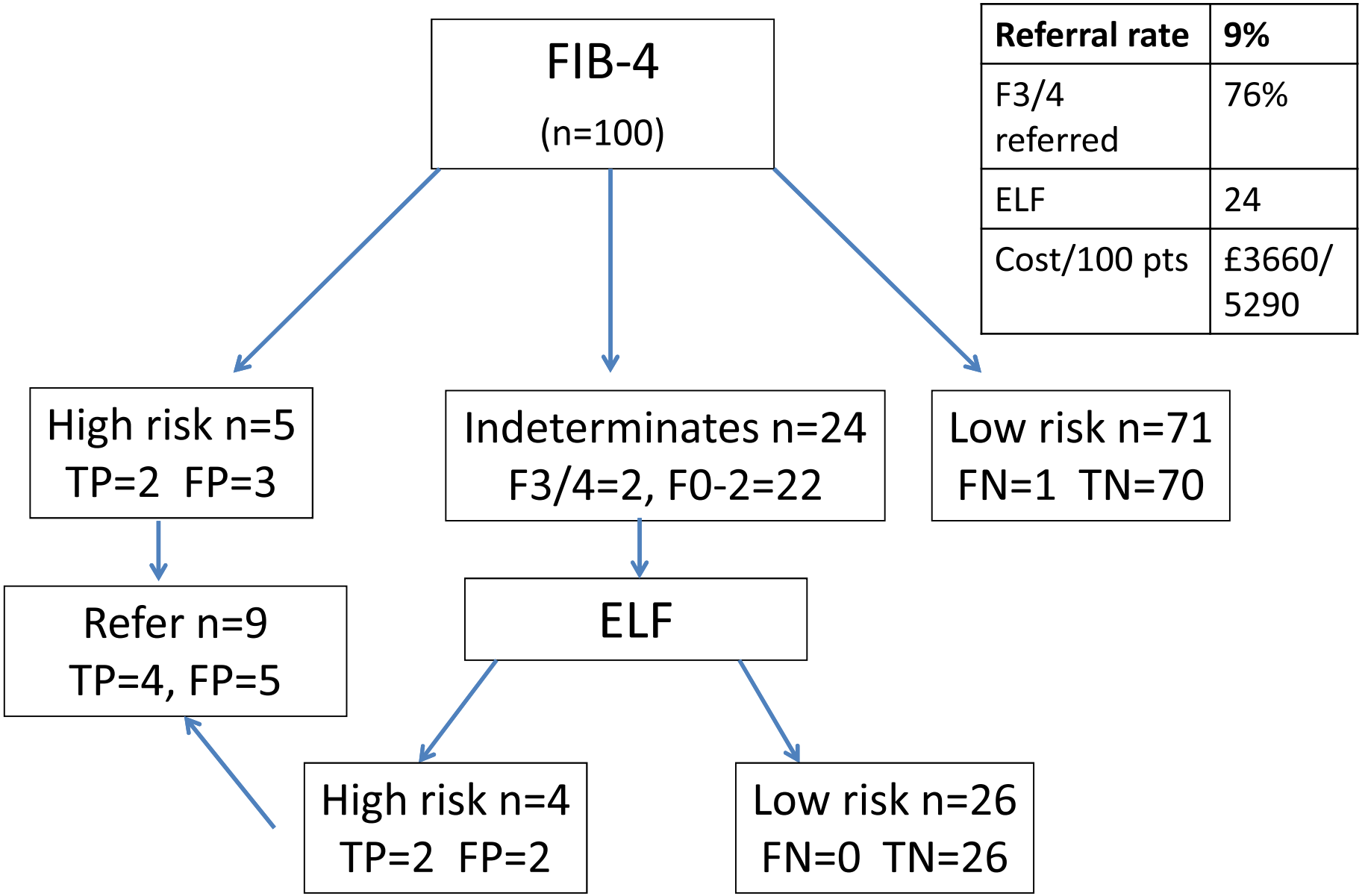
Referral rate	**29%**
F3/4 referred	84%
Cost/100 pts	£8700



Referral rate	**11%**
F3/4 referred	76%
Fibroscan	24
Cost/100 pts	£4520

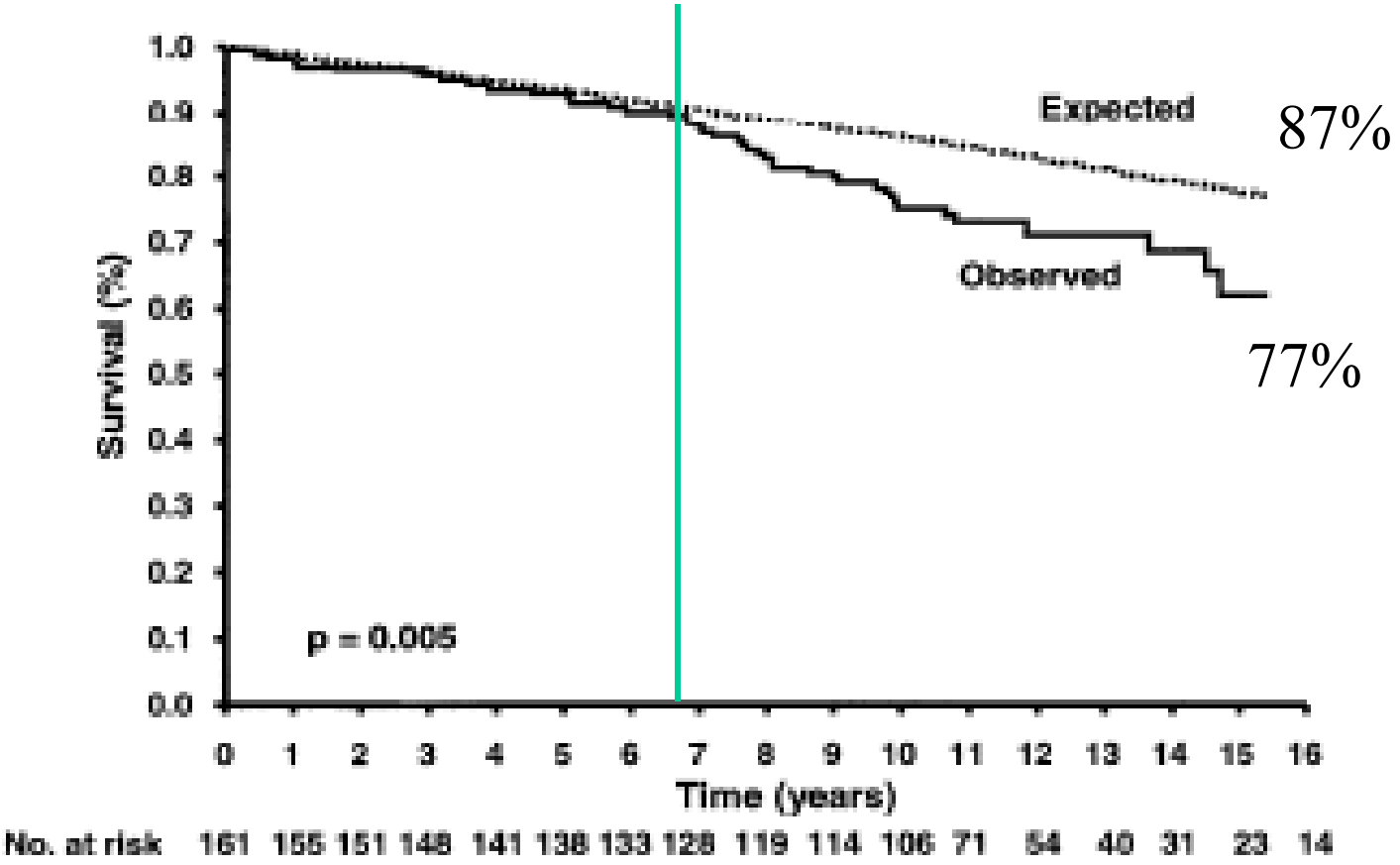


Referral rate	**13%**
F3/4 referred	78%
Fibrotest	24
Cost/100 pts	£4950



Referral rate	**9%**
F3/4 referred	76%
ELF	24
Cost/100 pts	£3660/ 5290

Natural history of NAFLD

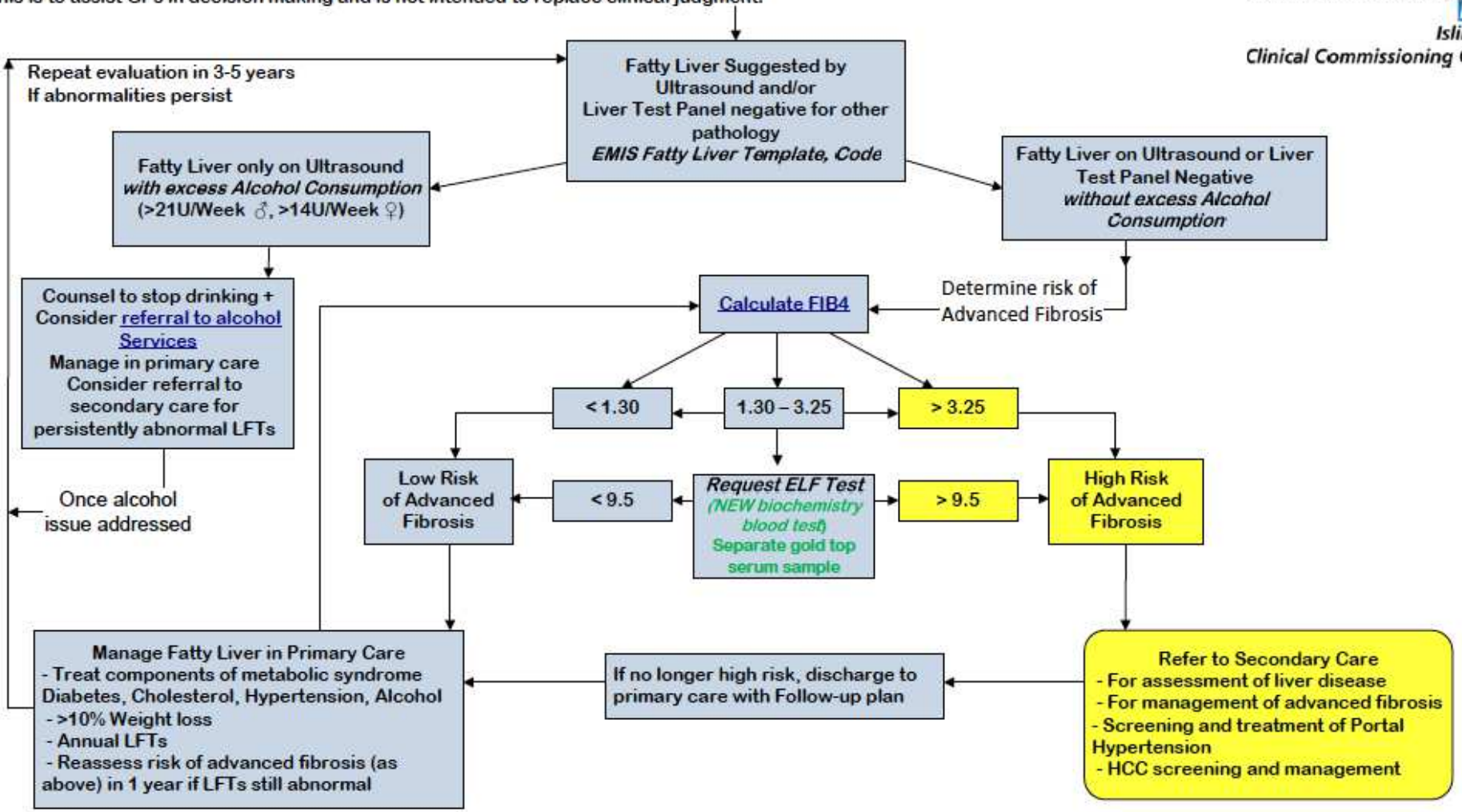


420 patients
Mean follow up 7.6 years

Adams, Gastro 2005

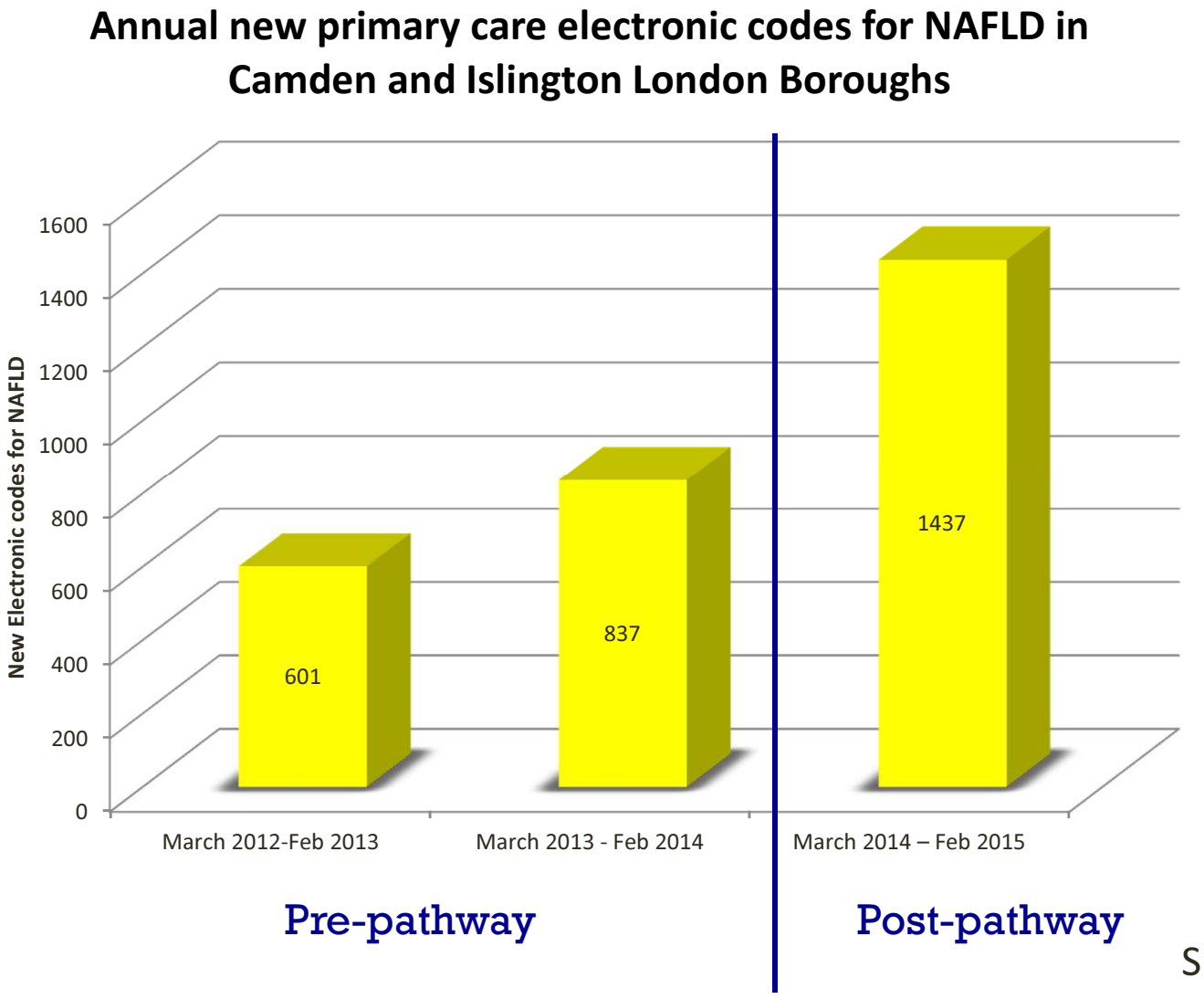
Abnormal Liver Function Tests Guidance
This guidance has been developed in collaboration with local specialists in Camden and Islington.
This is to assist GPs in decision making and is not intended to replace clinical judgment.

NHS Camden Clinical Commissioning Group
NHS Islington Clinical Commissioning Group



Annual new cases of NAFLD in C&I

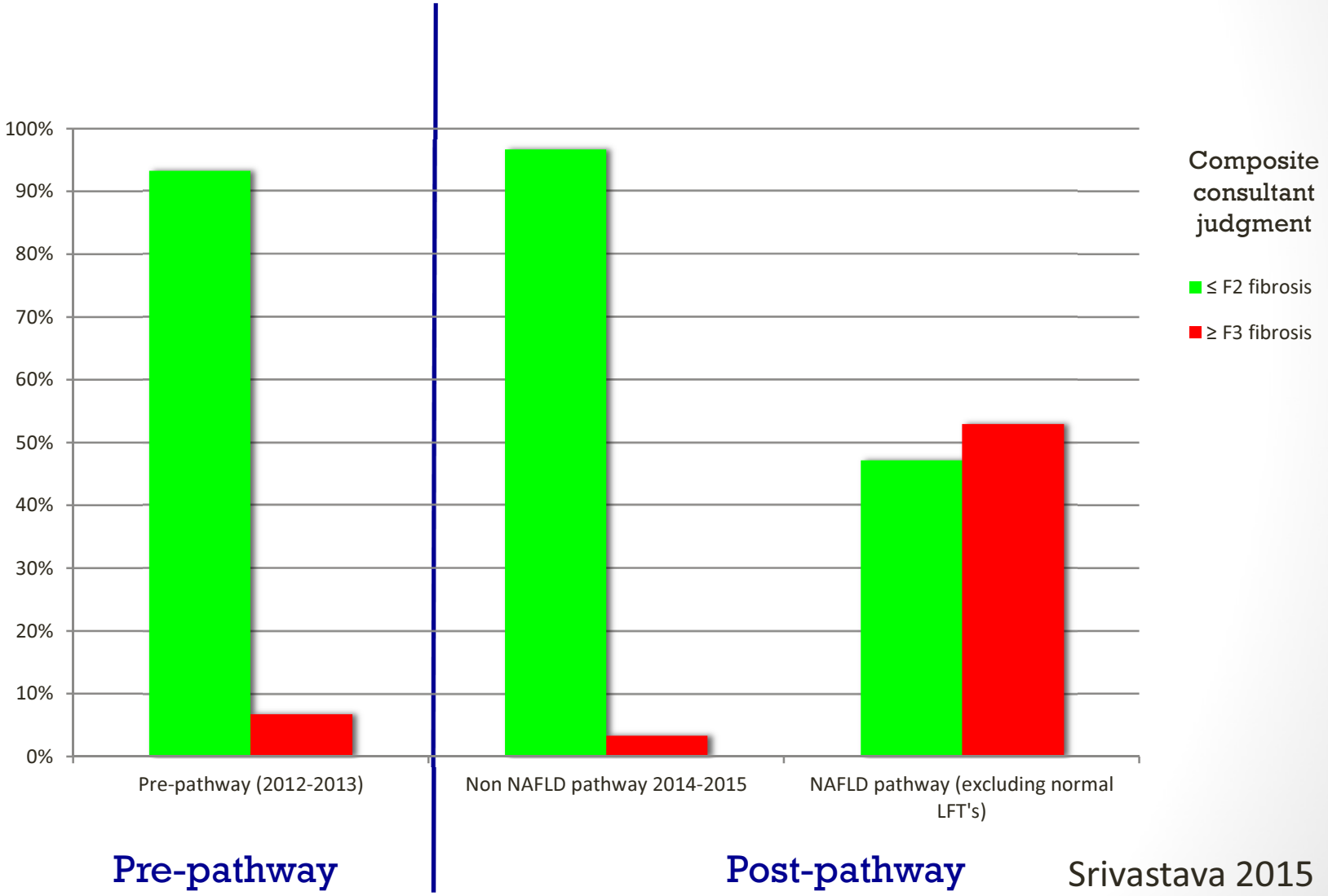
*population of Camden and Islington = 400,000



Srivastava 2015

Initial impact of pathway

*after evaluation of 40% of post pathway data at Royal Free London



Srivastava 2015

Treatment

Who should be treated?

Simple steatosis:

Lifestyle advice, CVS factors

NASH, F0-F1 fibrosis:

Lifestyle advice, CVS factors, clinical trials

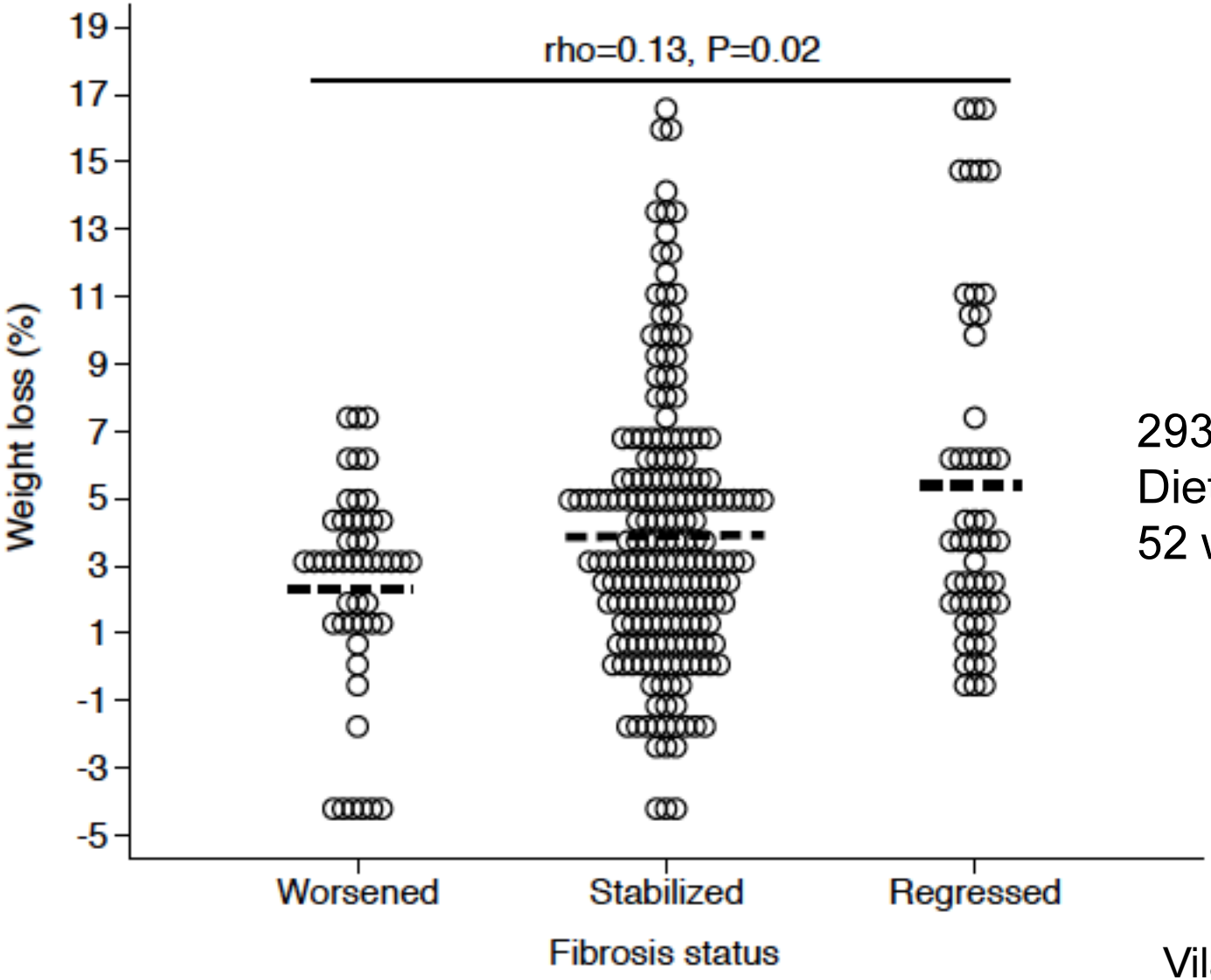
NASH, significant fibrosis:

Liver-specific interventions, clinical trials

Potential treatment targets

- Lifestyle changes
- Antioxidant factors
- Insulin resistance
- Fibrosis

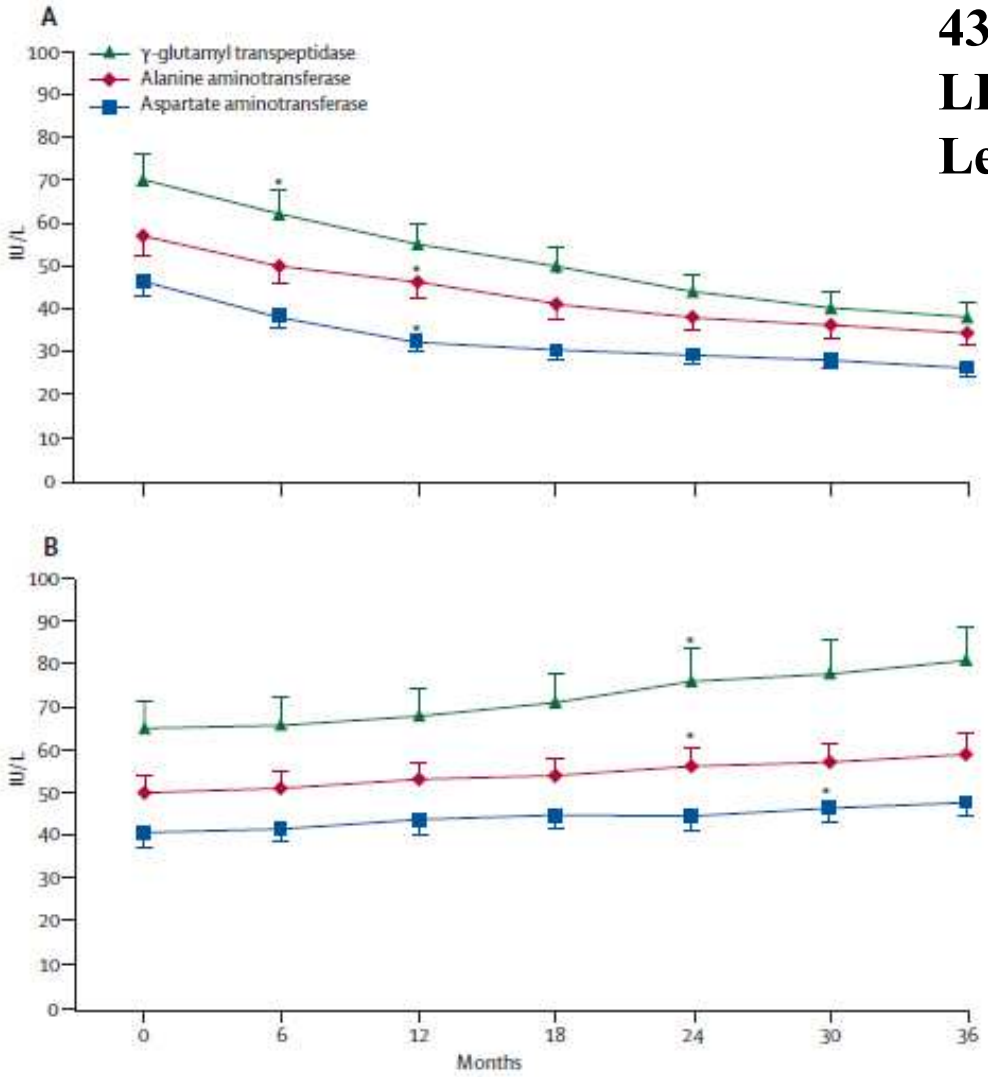
Weight loss and NASH



293 patients
Dietary intervention
52 weeks

Vila-Gomez Gastro 2015

Statins in liver disease

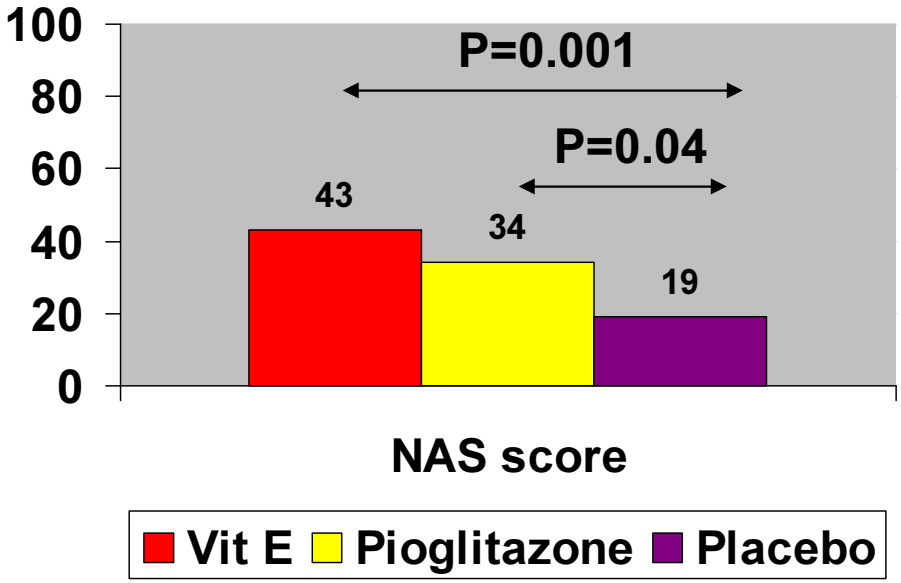


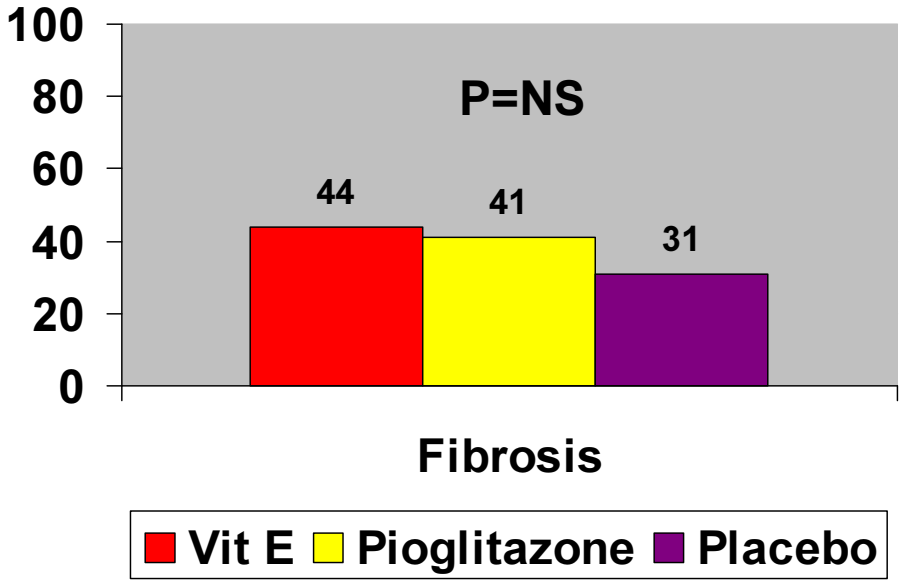
437 patients with abnormal LFTs
LFT improvement
Less CVS events

Athyros Lancet 2010

PIVENS
Pioglitazone, Vitamin E or placebo

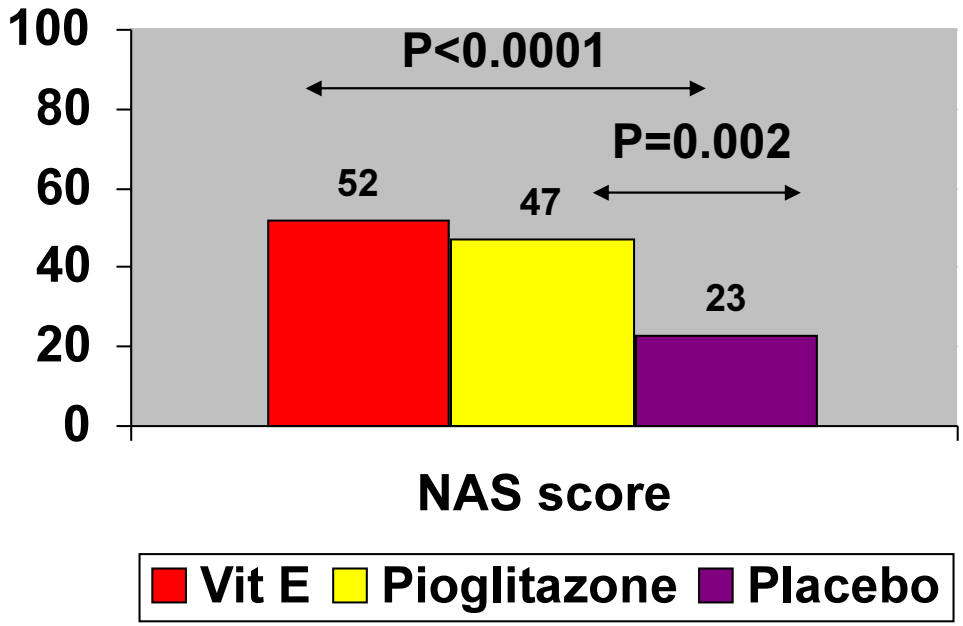
287 non-diabetic patients
2 years of treatment





Sanyal NEJM 2010

PIVENS
Per Protocol analysis



Patients with no ballooning after central pathology review

Vitamin E	**18%**
Pioglitazone	**28%**
Placebo	**17%**

Sanyal NEJM 2010

TONIC trial – metformin or Vitamin E in children or adolescents

Histological characteristic	Vit E (n=50)	Metformin (n=50)	Placebo (n=47)
Regression of NASH	**25 (56%)***	15 (41%)	11 (28%)
NAS score	**-1.8***	-1.1	-0.7
Improvement in fibrosis	18 (37%)	22 (44%)	19 (40%)
Improvement in ballooning	**22 (44%)***	**22 (44%)***	10 (21%)
Improvement in steatosis	27 (54%)	26 (52%)	19 (40%)

JAMA 2011

Vitamin E: current evidence

- Effective in two RCTs (PIVENS, TONIC)

BUT:

  - Increased mortality in doses >400 IU/day
  - Increased risk of prostate cancer

Lipid metabolism

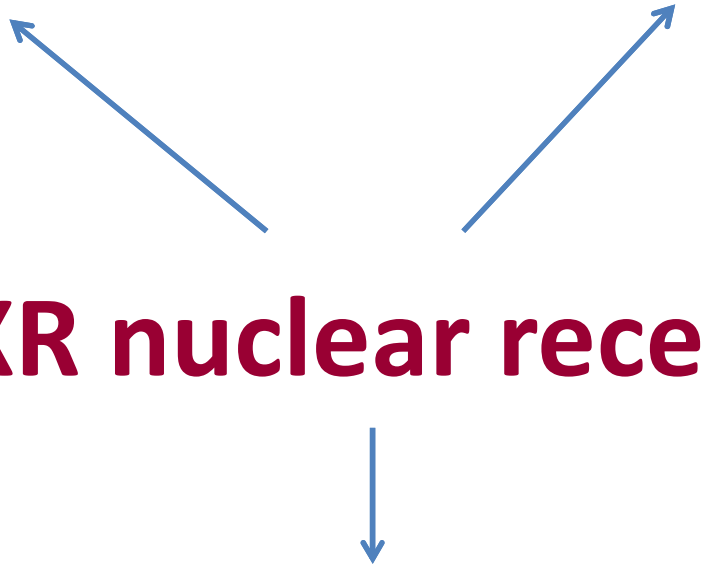
Reduces lipogenesis (SREBP1c)

Increases fatty acid oxidation

Carbohydrate metabolism

Improves insulin sensitivity

Reduces neoglucogenesis



FXR nuclear receptor

Liver

Reduces inflammation (NF-kB)

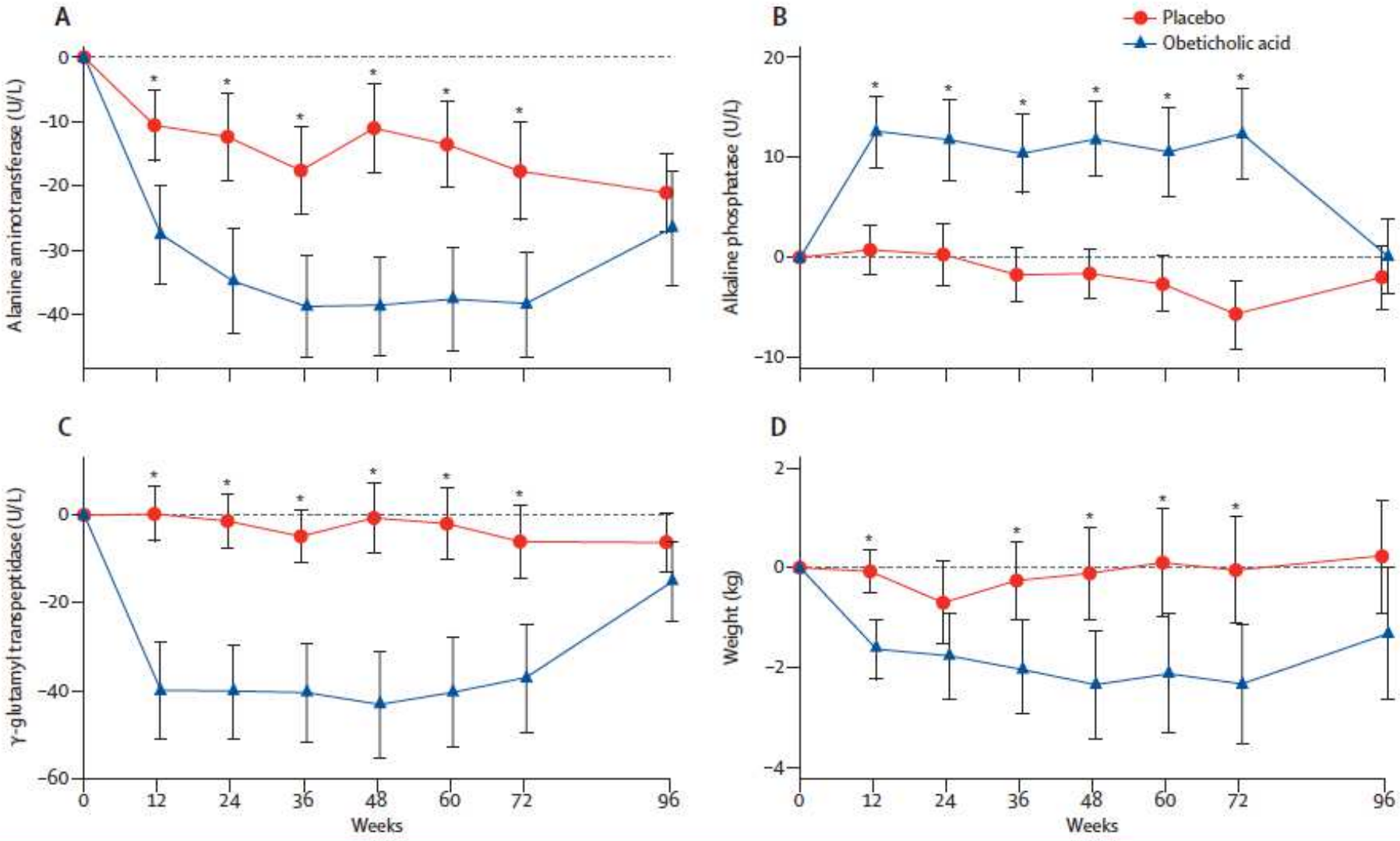
Antifibrotic

Obeticholic acid

- Farnesoid X receptor agonist
- Non-cirrhotic NASH
- Double blind, phase II, placebo controlled trial
- 25 mg OCA (n=141), placebo (n=142) 72 weeks
- Primary endpoint = 2 point improvement in NAS with no worsening of fibrosis
- Improvement in histology (50 OCA, 23 placebo)
- Increase in LDL

Neuschwander-Tetri Lancet 2014

Obeticholic acid – FXR ligand



Neuschwander-Tetri Lancet 2014

FLINT - histological data

Feature	OCA	Placebo	Relative Risk	P value
Number of patients	102	98		
Decrease of NAS score by ≥2 points with no worsening of fibrosis	50(45%)	23(21%)	1.9 (1.3-2.8)	0.0002
Improvement in Fibrosis	36(35%)	19(19%)	1.8(1.1-2.7)	0.004
Improvement in Ballooning	47(46%)	30(31%)	1.5(1.0-2.1)	0.03
Improvement in lobular inflammation	54(53%)	34(35%)	1.6(1.1-2.2)	0.006
Improvement in Steatosis	62(61%)	37(38%)	1.7(1.2-2.3)	0.001

LEAN – liraglutide vs. placebo

Feature	Liraglutide (n=23)	Placebo (n=22)	P
NASH regression	9 (39%)	2 (9%)	<0.05
NAS score	-1.3	-0.8	NS
Improvement in fibrosis	6 (26%)	3 (14%)	NS
Improvement in ballooning	14 (61%)	7 (32%)	NS
Improvement in steatosis	19 (83%)	10 (45%)	<0.05
Improvement in lobular inflammation	11 (48%)	12 (55%)	NS

Armstrong Lancet 2015

Treatment of metabolic syndrome components

- Obesity – exercise and diet
- T2DM– pioglitazone, metformin or liraglutide
- Hypertension – AAT2
- Dyslipidaemia – statins
- Smoking cessation

Management of NAFLD by the HIV physician

Follow-up in HIV clinic of patients at low risk of fibrosis

-Annual LFTs

- >10% weight loss

- Treat components of metabolic syndrome

(hypertension, diabetes, hyperlipidaemia)

- In 3-5 years re-assess risk of advanced fibrosis

using non-invasive fibrosis assessment

Conclusions

- 10% of HIV patients might have NAFLD with fibrosis
- Only a minority needs hepatology referral
- Not confined to the liver
- Aggressive treatment of MS components